NEW PYROLYTIC ROUTES TO FUSED BRIDGEHEAD NITROGEN HETEROCYCLES

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Dedication

This thesis is dedicated to my father who tirelessly dedicated himself to putting me here and to a good friend of mine who was robbed of his chance by circumstance. Here's to you two.

Acknowledgements

I would like to thank my supervisor Dr. Hamish McNab for his guidance, advice, encouragement and enthusiasm over the past four years.

I am grateful to the technical staff, in particular Mr. J. R. A. Millar (NMR), Mr. A. T. Taylor (mass spectroscopy), Mrs. L. J. Eades and Mrs. S. Djurdjevic (elemental analysis) and Dr. R. O. Gould and Dr. S. Parsons (crystallography), for their help and without whom this thesis would not have been possible.

Thanks also to the members of the research group, both past and present, who have made my time in the laboratory highly enjoyable.

Finally, my thanks go to my friends and family, in particular my better half Julia for putting up with me for the duration of this work and my father for making sure help was available in the form of support, advice and 'The Bank of Dad'.

Lecture courses attended

The following lecture courses were attended during the period of my research:

1. Safety Workshop Edinburgh, Sigma-Aldrich, School of Chemistry, University of Edinburgh.
2. Organic Research Seminars, School of Chemistry, University of Edinburgh (3 years attendance).
3. Departmental Organic Colloquia, School of Chemistry, University of Edinburgh (3 years attendance).
4. Royal Society of Chemistry, Perkin Divisional Meeting (3 years attendance).
5. Royal Society of Chemistry, Perkin Division, RSC-SCI Joint Meeting on Heterocyclic Chemistry, Edinburgh (3 days).
6. Chemical Carcinogens – Dr. R. M. Paton (5 lectures).
7. Industrial Ecology – Prof. P. Tasker (5 lectures).
8. Chemical Evolution – Dr. M. Heal (5 lectures).
9. Inorganic Materials – Dr. C. Pulham (5 lectures).
10. Molecular Machines – Prof. D. A. Leigh (5 lectures).
11. Postgraduate 3rd year seminars, University of Edinburgh at Firbush.

Abstract

Under flash vacuum pyrolysis (FVP) conditions *C*-unsubstituted imidazole *N*-propenoate ester derivatives give 78±5:22±5 mixtures of pyrrolo[1,2-*a*]imidazol-5-one and pyrrolo[1,2-*c*]imidazol-5-ones. The mechanism involves a cascade process initiated by 1,5-sigmatropic shift of the substituent. Substitution of the imidazole *N*-propenoate ester at the 2-position or 4,5-positions of the heterocycle allows exclusive access to the pyrrolo[1,2-*c*]imidazol-5-one and pyrrolo[1,2-*a*]imidazol-5-one systems respectively upon FVP. Ring-opening of the pyrrolo[1,2-*c*]imidazol-5-one system in THF/water readily affords *cis*-urocanic acids [formally *cis*-3-(imidazo-4-yl)-acrylic acids].

A number of novel pyrrolo[1,2-*a*]indol-3-ones and pyrrolo[1,2-*a*]benzimidazol-1-ones have been prepared by a similar strategy involving FVP of indole or benzimidazole propenoate or *N*-benzoate ester derivatives. Pyrrolo[1,2-*a*]indol-3-ones have been obtained by complementary pyrolyses of indole 3-propenoates and *N*-propenoates and pyrolyses of indole *N*-benzoates affords the isoindolo[2,1-*a*]indol-6-one system. The pyrrolo[1,2-*a*]indol-3-ones are stable at room temperature whereas pyrrolo[1,2-*a*]benzimidazol-1-ones are much less so.

The reactions of the new heterocyclic systems were studied. Thus, hydrogenation of pyrrolo[1,2-*a*]indol-3-one at medium pressure affords largely 1,2-dihydropyrrolo[1,2-*a*]indol-3-one whereas pyrrolo[1,2-*a*]benzimidazol-1-one affords 1,2-dihydropyrrolo[1,2-*a*]benzimidazol-1-one and 2-ethylbenzimidazole. High pressure hydrogenation of pyrrolo[1,2-*a*]indol-3-one gives a range of hydrogenation products although complete hydrogenation has been achieved over 8 h for 11-methylisoindolo[2,1-*a*]indol-6-one.

Diels-Alder cycloaddition reactions of pyrrolo[1,2-*a*]indol-3-one and pyrrolo[1,2-*a*]benzimidazol-1-one with isobenzofuran and with cyclopentadiene afford exclusively the *endo* adduct in each case. The reaction of pyrrolo[1,2-*a*]indol-3-one with 4-methoxybenzyl azide gives a 1,2,3-triazolo-adduct with high regioselectivity.

The reaction of pyrrolo[1,2-*a*]indol-3-ones with a range of nucleophiles has been studied. Treatment with 'hard' nucleophiles (methoxide and $LiAlH_4$) gives ring-opening at the 'hard' carbonyl electrophilic centre whereas treatment with a 'soft'

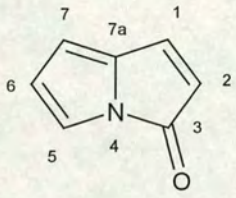
nucleophile (thiophenol) gives addition at the 1-position. Primary amines afford no addition product with pyrrolo[1,2-*a*]indol-3-ones and the addition of piperidine is solvent sensitive affording exclusively addition product in acetone but mixtures of addition and methoxide ring-opened products in methanol.

Contents

INTRODUCTION

Introduction

This introduction aims to review the synthetic preparations, chemical reactivity and physical properties of pyrrolizin-3-ones **1** and associated annulated tricyclic benzopyrrolizin-3-ones **2** and tetracyclic dibenzopyrrolizin-3-ones **3**. These classes of compound are not particularly well documented although some targeted synthesis has been performed and these routes generally involve formation of the pyrrolone ring and to a lesser extent pyrrole ring formation. A few miscellaneous examples involve dehydrogenation to form the enone double bond and others photooxidation of the fully reduced lactam unit.



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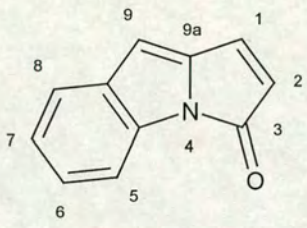

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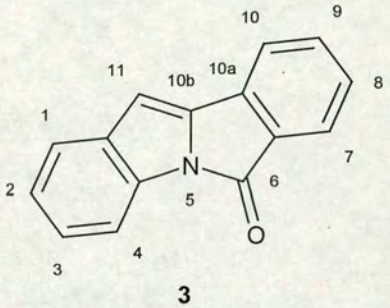

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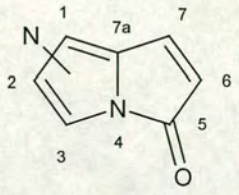
Use of the unqualified terms 'pyrrolizinone', 'benzopyrrolizinone' and 'dibenzopyrrolizin-3-one' refers solely to the 3-one isomers in this thesis.

Numbering schemes for the parent pyrroloimidazolones and azabenzopyrrolizinone systems are shown below.



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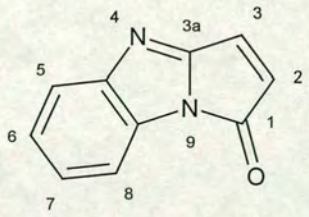

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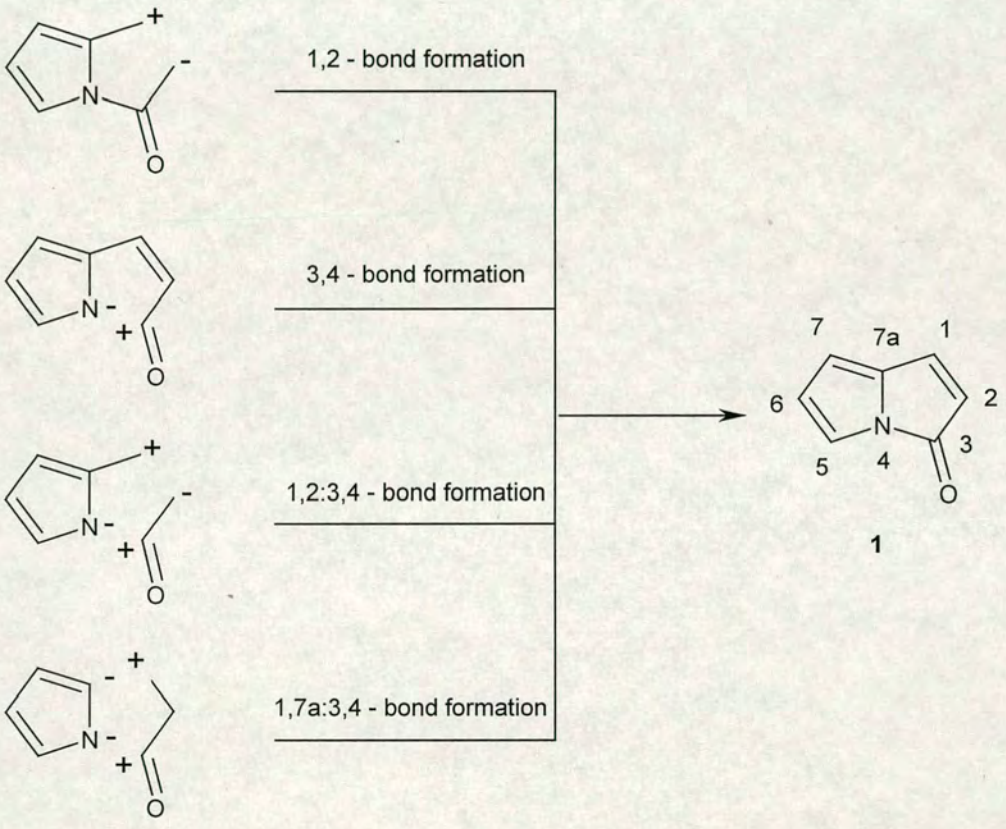
1.1 Synthesis

1.1.1 Pyrrolizin-3-one synthesis

Relatively little attention has been paid to the pyrrolizin-3-one system and all work up to 1993 is comprehensively covered in a previous review.[01] The routes herein cover new synthetic methods published after 1993. The synthesis of pyrrolizin-3-ones **1** usually begins with a simple pyrrole. The synthetic routes are best classified by the number and position of bonds formed in the ring-closure step.

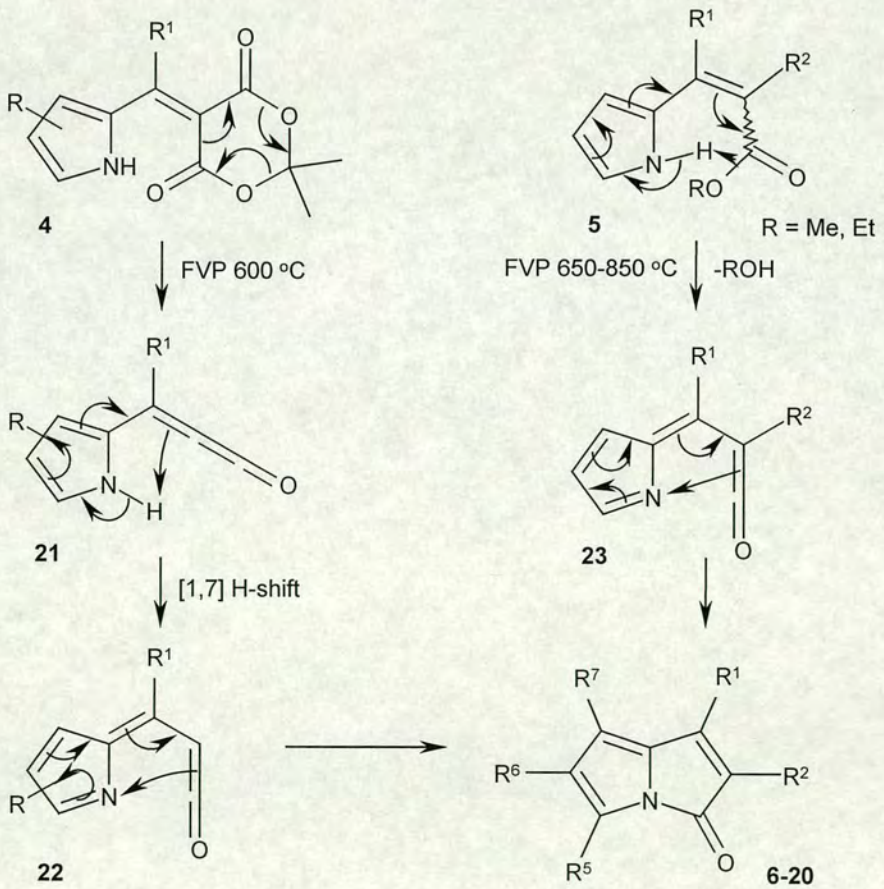


Little synthetic work has been done since 1993 but the most important recently developed routes involve flash vacuum pyrolysis (FVP) methods and the reaction of 2-formylpyrroles with hydrocinnamoyl chloride.

1.1.1.1 3,4-Bond formation by flash vacuum pyrolysis

Pyrrolizin-3-ones can be efficiently synthesised from Meldrum's acid derivatives **4** and pyrrolylpropenoates **5** in good yields (Scheme 1).

Knoevenagel condensations of 2-formylpyrroles (or 2-acetylpyrrole where R^1 = Me) with 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) or reactions of pyrroles with 5-methoxymethylene-2,2-dimethyl-1,3-dioxane-4,6-dione (methoxymethylene Meldrum's acid) give useful precursors that under flash vacuum pyrolysis conditions yield pyrrolizin-3-ones. The method has been applied to the preparation of various monosubstituted pyrrolizin-3-ones **6-16** (Table 1). Products are formed by the generation of a methyleneketene intermediate **21** that undergoes a [1,7] hydrogen shift to the ketene **22** followed by intramolecular electrocyclic *N*-acylation to the lactam **6-16**.[02]



Scheme 1

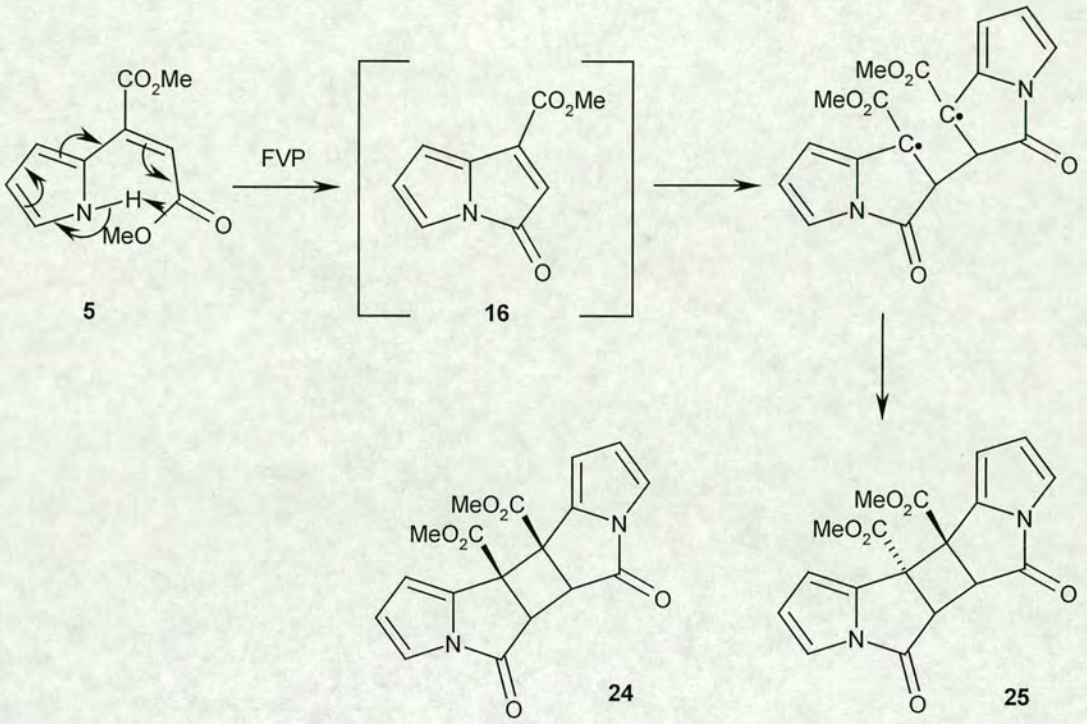
	R^1	R^2	R^5	R^6	R^7	Yield (%)	Ref.
6	H	H	H	H	H	88	**03**
7	Me	H	H	H	H	73	**04**
8	H	H	Me	H	H	87	**04**
9	H	H	Ph	H	H	88	**04**
10	H	H	CO_2Et	H	H	69	**04**
11	H	H	H	H	Me	96	**05**
12	H	H	H	H	OMe	37	**04**
13	H	H	H	H	CO_2Me	81	**04**
14	H	H	H	H	CH_2OAc	90	**05,06**
15	H	H	H	Ph	Ph	84 (mixture)	**04**
16	CO_2Me	H	H	H	H	-	**07**
17	H	Me	H	H	H	87	**04**
18	H	CN	H	H	H	81	**04**
19	H	COMe	H	H	H	76	**04**
20	H	CO_2Me	H	H	H	84	**04**

Table 1 – Pyrrolizin-3-one synthesis from Meldrum's acid derivatives and from pyrrolylpropenoates

2-Substituted pyrrolizin-3-ones **17-20** cannot be generated from Meldrum's acid derivatives due to the requirement for a [1,7] hydrogen shift but such a problem can be overcome by the use of pyrrolylpropenoate precursors **5** that are easily synthesised using Wittig or Knoevenagel conditions. Pyrolysis directly generates the ketene **23** *via* the loss of methanol and hence negates the requirement of a [1,7] hydrogen shift before the cyclisation to the pyrrolizin-3-one products **17-20** (Scheme 1).[04,05]

The FVP of **5** (where R = Me, $R^1 = CO_2Me$ and R^2 = H) is a special case and 1-methoxycarbonylpyrrolizin-3-one **16** can only be isolated by quenching at low

temperature (typically –20 °C) in a suitable solvent (chloroform, acetone or methanol). However, at room temperature 1-methoxycarbonylpyrrolizin-3-one **16** dimerises over *ca.* 24 h to give the [2+2] cycloadducts **24** and **25** in 66% overall yield. No such dimerisation has been observed previously and may occur *via* an intermediate stabilised radical (Scheme 2).[07]



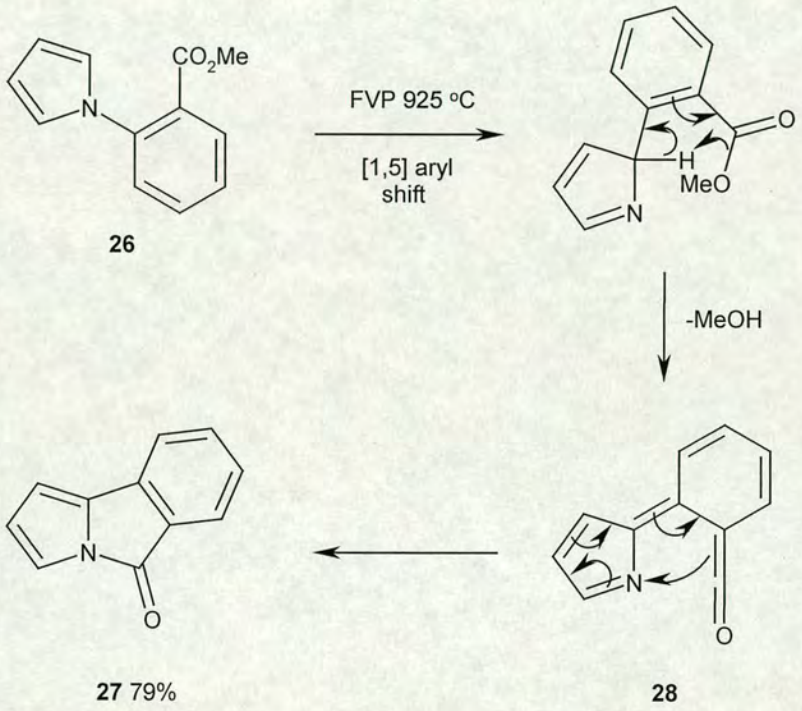
Scheme 2

1.1.1.2 3,4-Bond formation by flash vacuum pyrolysis cascade process

The thermal rearrangement of *N*-substituted pyrroles to 2- (and 3-) substituted isomers by sequential [1,5]-shifts has been known for some time.[08,09]

A further development in the flash vacuum pyrolysis technique has involved the recognition that these rearrangements, achieved under pyrolysis conditions, can be used in conjunction with the previously demonstrated electrocyclisation of 3-(pyrrol-2-yl)propenoate esters to generate pyrrolizin-3-ones *via* a cascade process.[10,04]

Pyrolysis of 1-(2-methoxycarbonylphenyl)pyrrole **26** at 925 °C affords pyrrolo[2,1-*a*]isoindol-5-one **27** in 79% yield *via* an initial [1,5]-aryl shift followed by the concerted elimination of methanol and electrocyclisation of the resulting ketene intermediate **28** (Scheme 3). It is suggested that the lack of any products derived from a 3-arylpyrrole indicates that the elimination/electrocyclisation is fast relative to the initial [1,5]-aryl shift. This method requires a higher temperature to effect the initial aryl migration than is required for the elimination-cyclisation alone. [11]

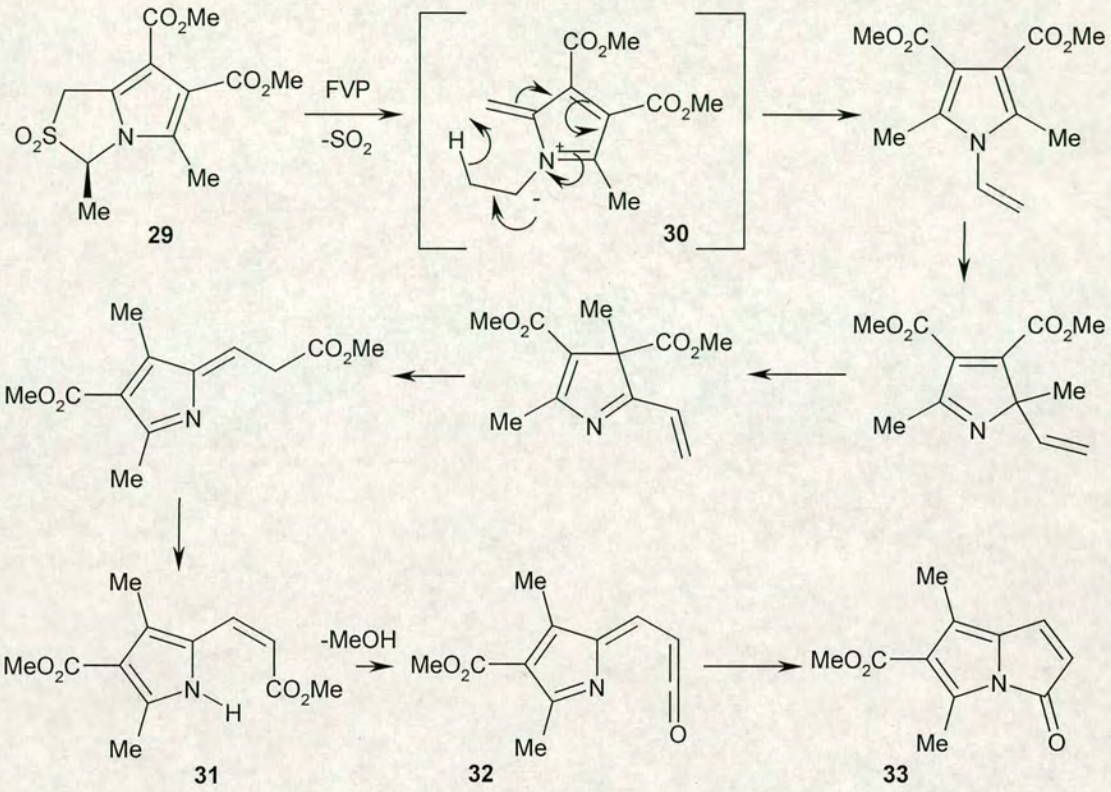


Scheme 3

1.1.1.3 3,4-Bond formation by flash vacuum pyrolysis of 3-methyl-5-methyl-1*H*-pyrrolo[1,2-*c*]thiazole-2,2-dioxide

Flash vacuum pyrolysis at 700 °C of 3-methyl-5-methyl-1*H*-pyrrolo[1,2-*c*]thiazole-2,2-dioxide **29** leads to the vinylpyrrole **30** by extrusion of sulfur dioxide and a [1,8] hydrogen shift in the 8π 1,7-dipolar system. Nitrogen to C-2 vinyl migration followed by C-2 to C-3 methyl migration and carbomethoxy rearrangement generates the pyrrole 2-propenoate **31** that electrocyclises *via* the ketene **32** with the loss of

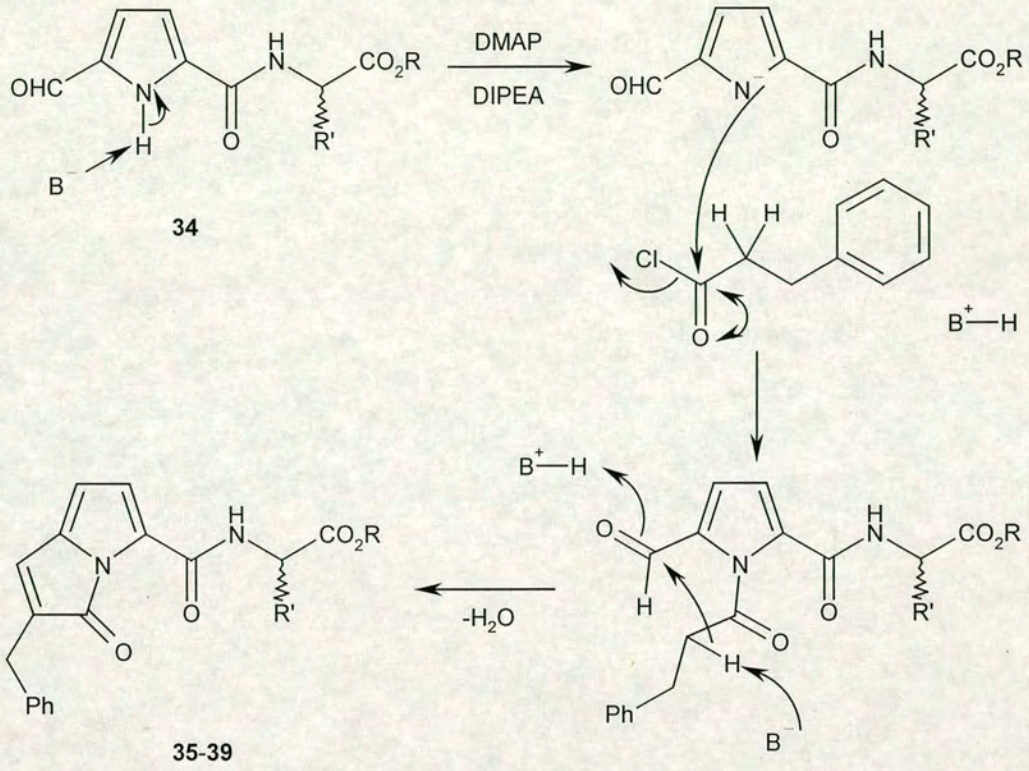
methanol leading to 1,3-dimethyl-5-oxo-5*H*-pyrrolizine-2-carboxylate **33** (Scheme 4).[12]



Scheme 4

1.1.1.4 1,2:3,4-Bond formation

In developing molecular tags for solid phase labelling of compounds, Abell *et al* used the reaction of 5-formylpyrroles with hydrocinnamoyl chloride to generate vibrant red pyrrolizin-3-one tags.[13] Hydrocinnamoyl chloride was added to dichloromethane solutions of 5-formyl-1*H*-pyrrole-2-carboxylic acids **34** in the presence of diisopropylethylamine and a catalytic amount of 4-dimethylaminopyridine and stirred at room temperature for 24 h. The authors assume that the reaction proceeds *via* *N*-acylation of the 5-formyl-1*H*-pyrrole-2-carboxylic acid with subsequent intramolecular aldol-type condensation to afford the pyrrolizin-3-ones **35-39** (Scheme 5).

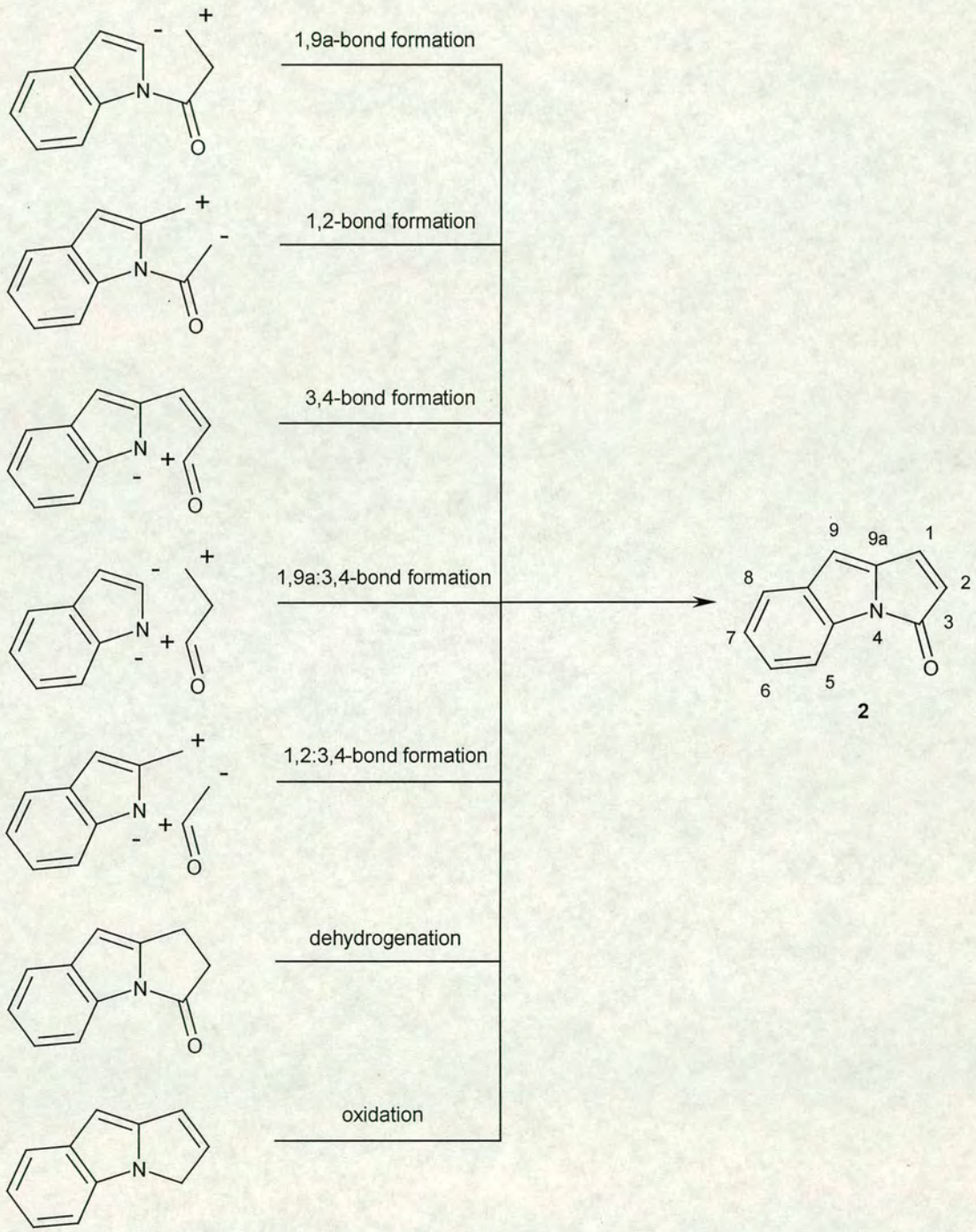


35 R = H, R' = Et 58%, **36** R = Me, R' = Me 21%, **37** R = CH_2CHMe_2, R' = Me 55%, **38** R = $CHMe_2$, R' = Me 35%, **39** R = CH_2Ph, R' = Me 58%

Scheme 5

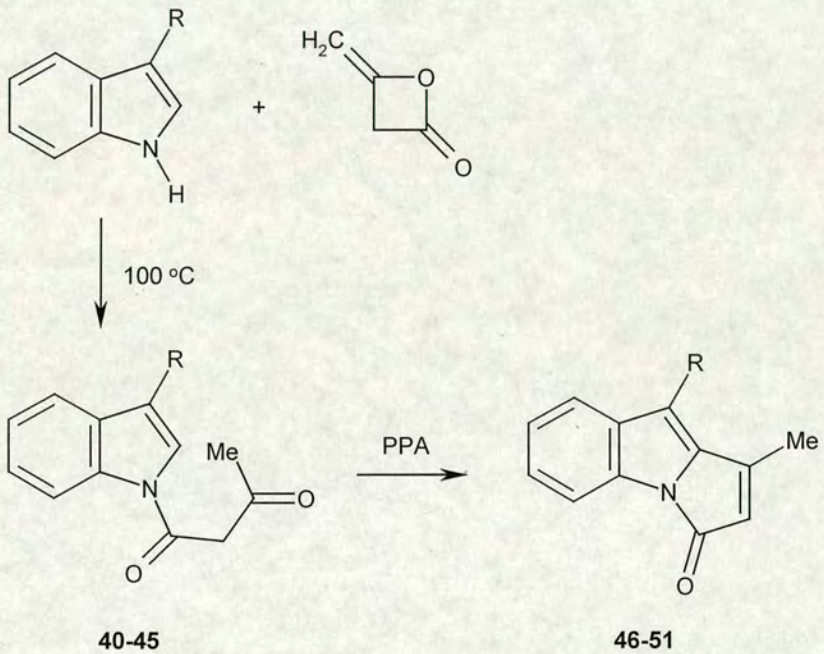
1.1.2 Synthesis of benzopyrrolizin-3-ones

In the benzopyrrolizin-3-one series, synthesis usually begins with an indole although 1-acetyl-3-indolinone and *N*-(2-bromomethylphenyl)succinimide have also been used. The synthetic routes are classified in a similar manner to those of the pyrrolizin-3-one series.



1.1.2.1 1,9a-Bond Formation

The only examples of 1,9a-bond formation in benzopyrrolizin-3-one synthesis are by Röder and Franke and involve a two-step reaction using 3-substituted indoles and diketene as the starting materials. Treatment of the 1-acetoacetylindoles **40-45** so obtained with polyphosphoric acid initiates ring closure to the benzopyrrolizinones **46-51** (Scheme 6). Overall yields range from 11-63%, but in the case of the 1-acetoacetyl-3-cyanomethyl indole **44**, acid hydrolysis of the cyano group occurs readily *via* protonation of the cyano nitrogen to generate to the amide **50** (Table 2).[14]

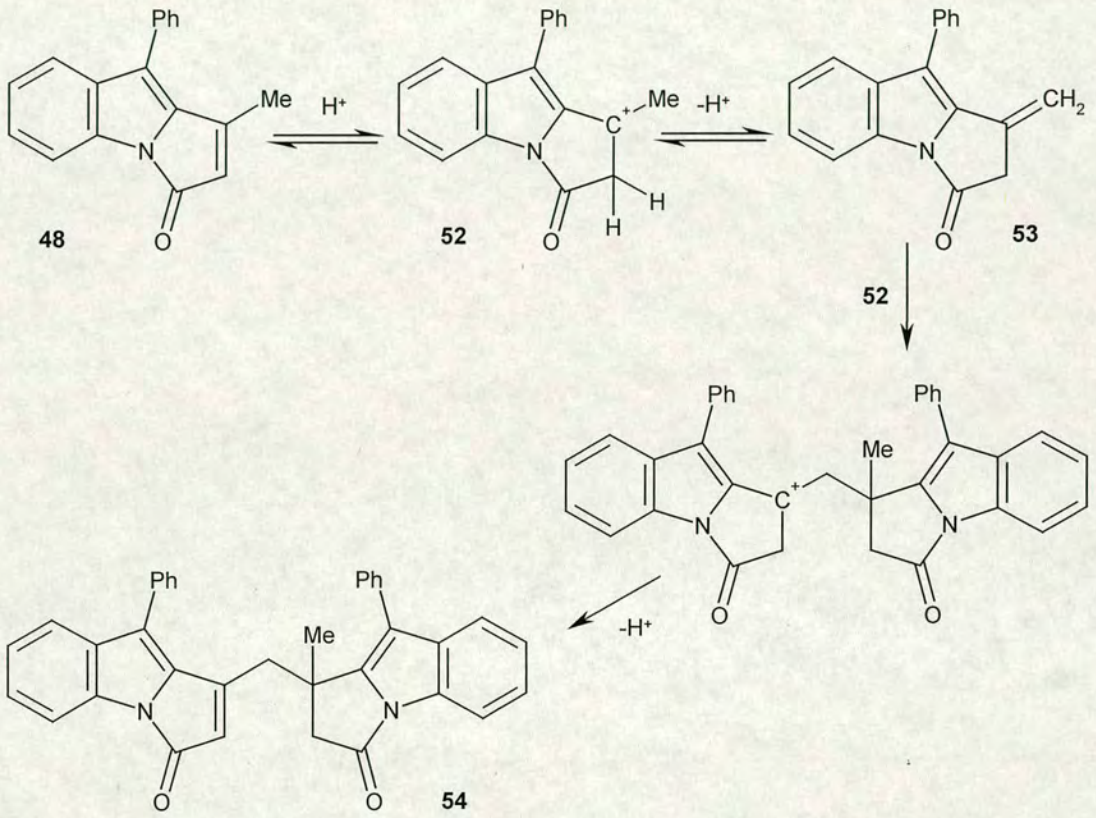


Scheme 6

	R	Yield (%)		R	Yield (%)
40	H	-	**46**	H	11
41	Me	70	**47**	Me	90
42	Phenyl	82	**48**	Phenyl	35
43	Benzyl	65	**49**	Benzyl	23
44	CH_2CN	50	**50**	CH_2CONH_2	60
45	$(CH_2)_2COCH_3$	27	**51**	$(CH_2)_2COCH_3$	73

Table 2 – Benzopyrrolizin-3-one from the reaction of indoles with diketene

In the presence of a small excess of polyphosphoric acid the cyclisation of **42** not only affords benzopyrrolizinone **48** but also a small amount of dimer. The process is initiated addition of a proton at the C-2 position of **48** to give the carbocation **52** which is in equilibrium with the methylene compound **53**. These two species undergo addition and combined with the subsequent loss of a proton generate the dimer **54** (Scheme 7).[15]



Scheme 7

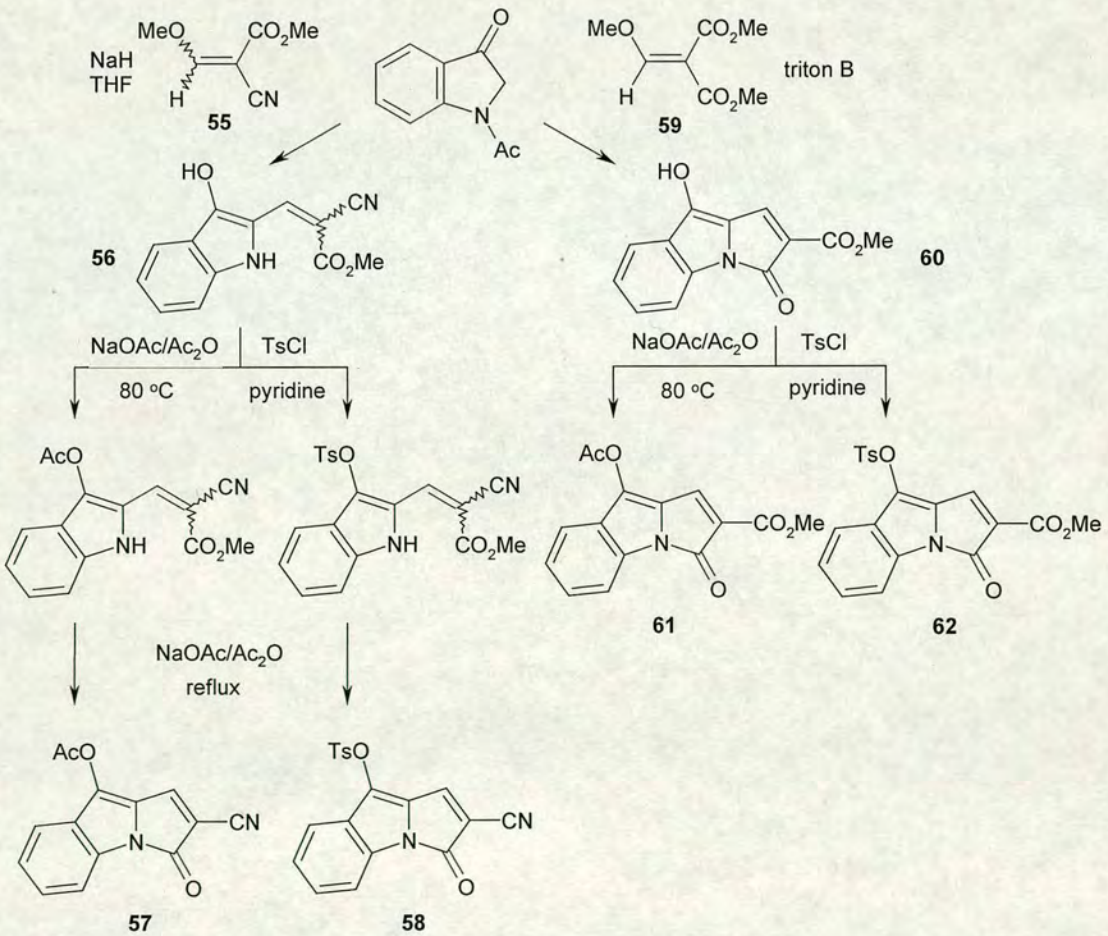
1.1.2.2 1,2-Bond formation

Whereas examples of 1,2-bond formation are documented in the pyrrolizin-3-one series no such example of benzopyrrolizin-3-one synthesis by 1,2-bond formation has been reported.[16]

1.1.2.3 3,4-Bond formation

1.1.2.3.1 Ring-closure by base

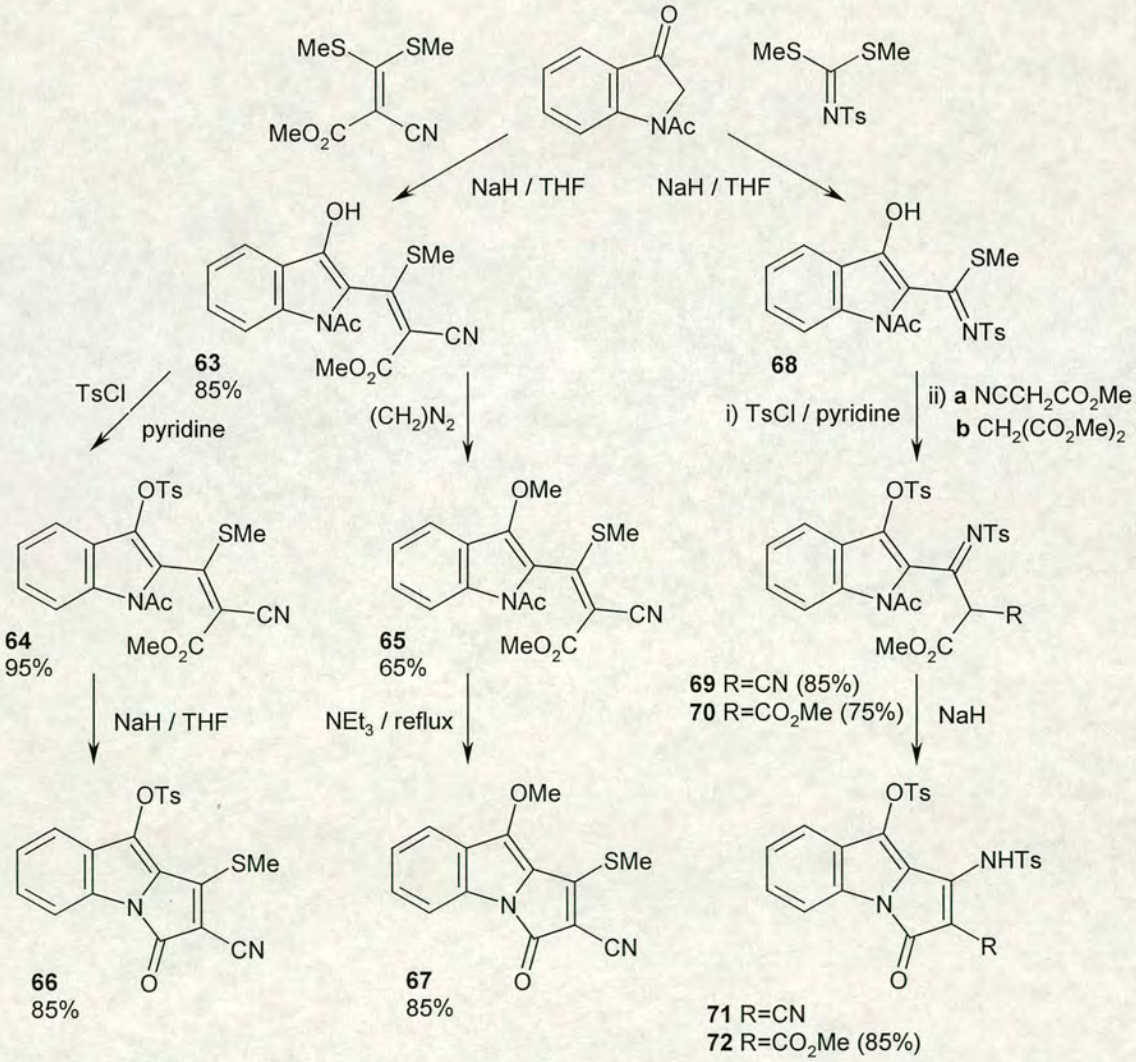
Mérour and Piroëlle found that reaction of 1-acetyl-3-indolinone with methyl 2-cyano-3-methoxypropenoate **55** in the presence of a 2-fold excess of sodium hydride followed by treatment with water affords the indole 2-propenoate **56** and that after protection of the hydroxyl group with acetic anhydride and sodium acetate or tosyl chloride and pyridine, heating at reflux in acetic anhydride with sodium acetate gave the benzopyrrolizin-3-ones **57** (52%) and **58** (59%) respectively. Similarly the use of methyl 2-methoxycarbonyl-3-methoxypropenoate **59** with triton B as base yields the 2-methoxycarbonylbenzopyrrolizin-3-one **60** (54%) directly and further treatment with acetic anhydride or tosyl chloride gives the analogous 2-methoxycarbonylbenzopyrrolizin-3-ones **61** (50%) and **62** (30%) (Scheme 8).[16]



Scheme 8

Tominaga *et al* studied the reaction of 1-acetyl-3-indolinone with 1-cyano-2,2-bis(methylthio)acrylate and with *N*-bis(methylthio)methylenebenzenesulfonamide. The reaction of **63** with tosyl chloride or diazomethane leads to tosyloxy and methoxy substituents respectively. Treatment of **64** with sodium hydride and **65** with triethylamine leads to *N*-acetyl deprotection and cyclisation to the products **66** and **67** respectively (Scheme 9).[17]

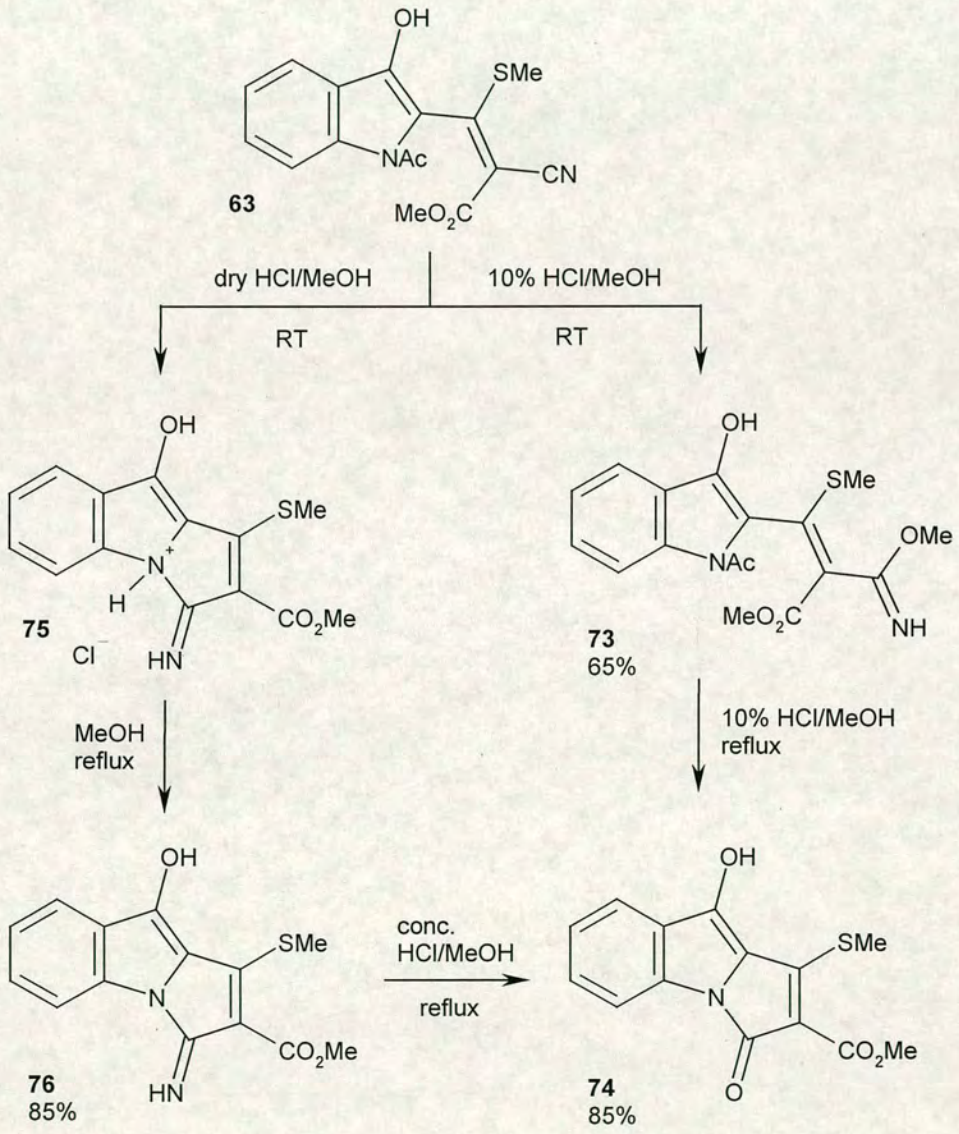
The reaction of **68** with active methylene compounds (*e.g.* **a**,**b** in Scheme 9) in the presence of potassium carbonate as base affords the substitution products corresponding to the reagent used. Cyclisation to the benzopyrrolizinones **71**-**72** is again achieved by treatment with sodium hydride (Scheme 9).[18]



Scheme 9

1.1.2.3.2 Ring-closure by acid

Tominaga *et al* also demonstrated that ring-closure can be initiated by acid. Treatment of **63** with 10% hydrochloric acid in methanol at room temperature leads to the addition of methanol across the cyano functionality to give **73**. By the use of more forcing conditions, heating under reflux, cyclisation to the tricycle **74** is achieved (Scheme 10). These conditions afford a methyl ester substituent at the 2-position as opposed to the cyano group obtained under basic conditions.[19]

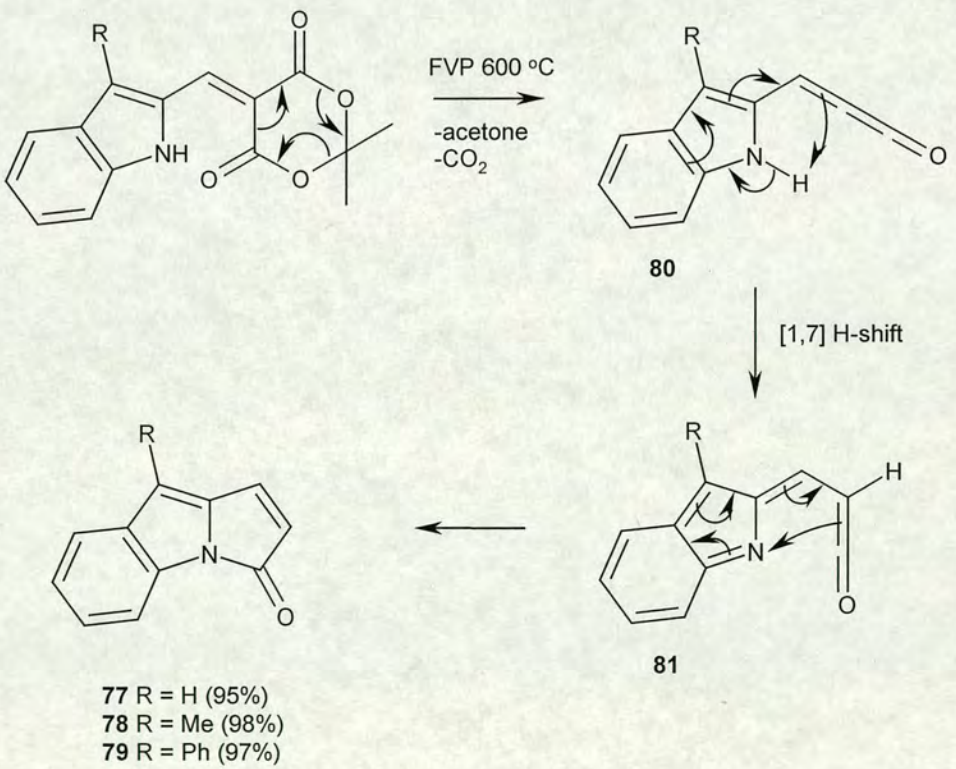


Scheme 10

Alternatively treatment of **63** with dry hydrogen chloride gas in methanol effects cyclisation to the tricycle hydrochloride **75** which after isolation can be heated at reflux in methanol to release the base affording **76**. Subsequent isolation of **76** and treatment with concentrated hydrochloric acid in methanol solution at reflux hydrolyses the imine to give **74**.[17]

1.1.2.3.3 Flash vacuum pyrolysis

The method employed in pyrrolizin-3-one synthesis (see section 2.1.1) has been used to good effect in the synthesis of benzopyrrolizin-3-ones.[19,20] Condensations of 2-formylindoles with 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) give suitable precursors that under flash vacuum pyrolysis conditions afford benzopyrrolizin-3-ones **77-79** in high yields (Scheme 11). As in the pyrrolizin-3-ones, the initially generated methyleneketene intermediate **80** undergoes a [1,7] hydrogen shift to the ketene **81** and intramolecular *N*-acylation to the lactam.



Scheme 11

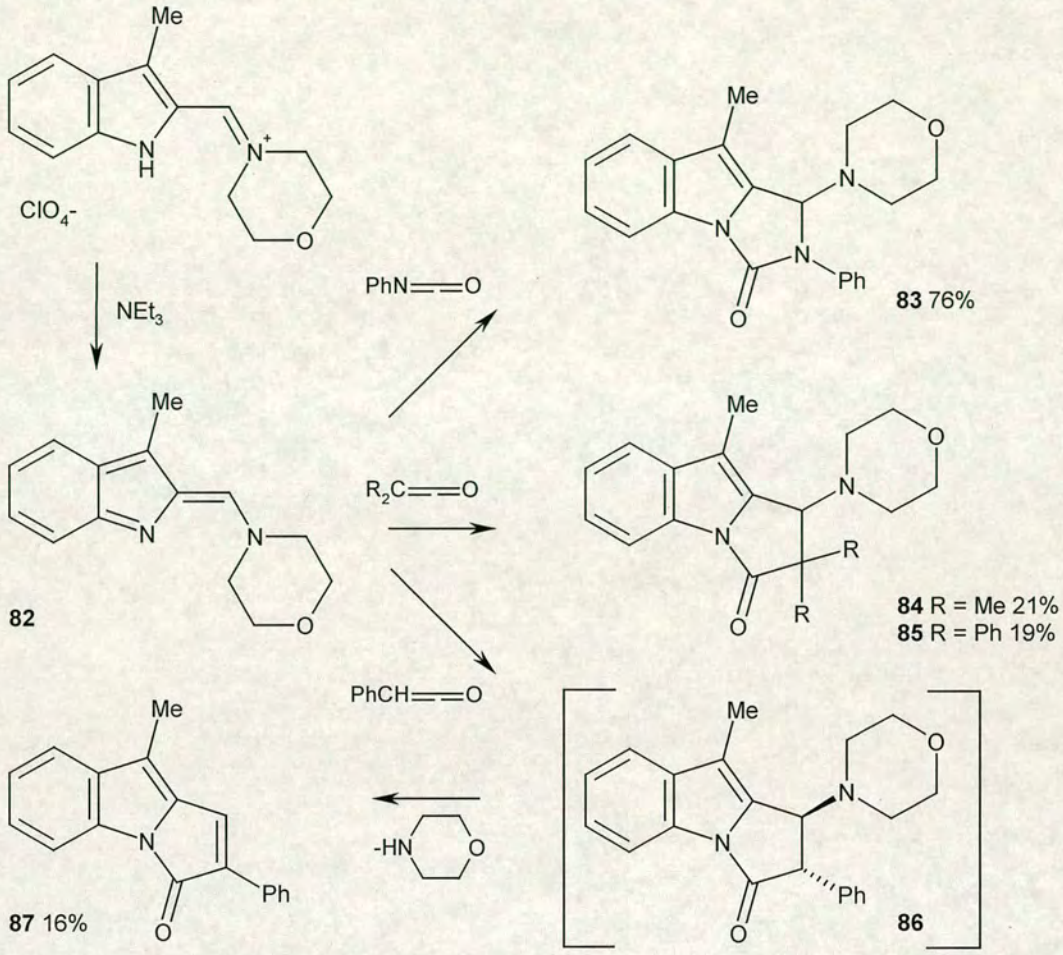
Whilst the cyclisation above is efficient, the overall route is hindered by the difficulty in 2-formylindole synthesis. Literature methods have several steps often involving selective reduction of indole-2-carboxylic acid and hence a more efficient precursor synthesis or an alternate precursor is required.[21]

1.1.2.4 1,2:3,4-Bond Formation

Only two examples of 1,2:3,4 bond formation are documented, one of which involves ketene type reagents and the other a phosphorane reagent.

1.1.2.4.1 Ketene reagents

Kobayashi *et al* found that 3-methyl-2-morpholin-4-ylmethylene-2*H*-indole **82**, liberated from the perchlorate with triethylamine, undergoes concerted [6+2] cycloadditions of phenylisocyanate, dimethylketene, diphenylketene and phenylketene to give the 1,2-dihydro cycloadducts **83-86**. However, the authors suggest that in the case of **86** the *trans* conformation of the morpholine and phenyl substituents allows elimination of the morpholine group to occur giving 2-phenyl-9-methylpyrrolo[1,2-*a*]indol-3-one **87** (Scheme 12).[22] There is no supporting spectroscopic data for the assignment of the *trans* conformation of **86** and the elimination is surprising because there is usually the need for the proton and leaving group to adopt a *trans* conformation for elimination to take place.

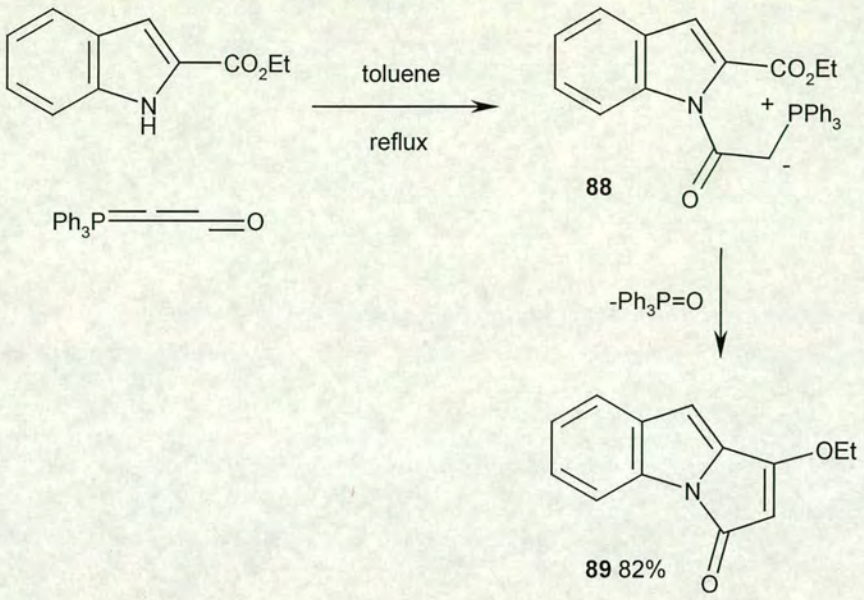


Scheme 12

In these reactions the cycloadditions are performed in the presence of base triggering the formation of the indol-2-ylidene species **82** which acts as a 10π electron component for the cycloaddition.

1.1.2.4.2 Phosphacumulene ylide reagent

Indole-2-carboxylic acid ethyl ester combines with triphenylphosphoranylidene ethenone in the absence of base to give the phosphorane **88** that cyclises by an intramolecular Wittig reaction to form 1-ethoxypyrrolo[1,2-*a*]indol-3-one **89** (Scheme 13).[23,24]

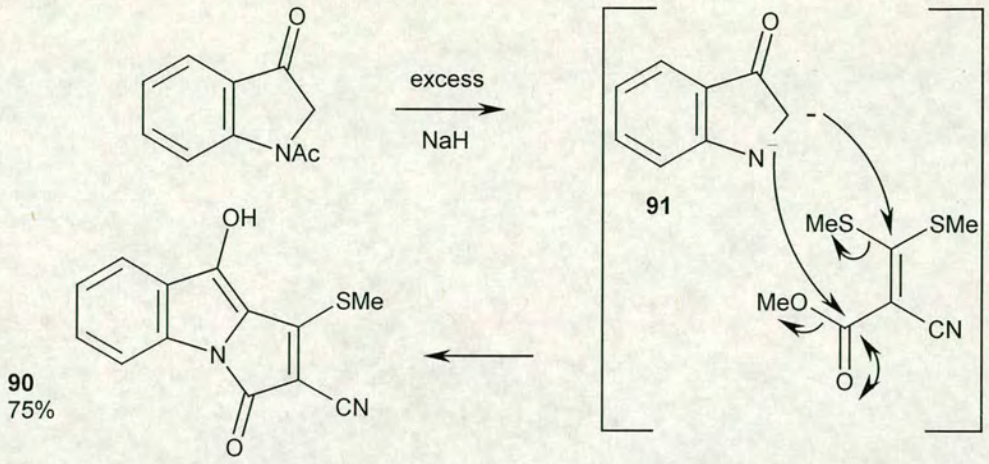


Scheme 13

1.1.2.5 1,9a:3,4-Bond formation

1.1.2.5.1 Amide formation by base

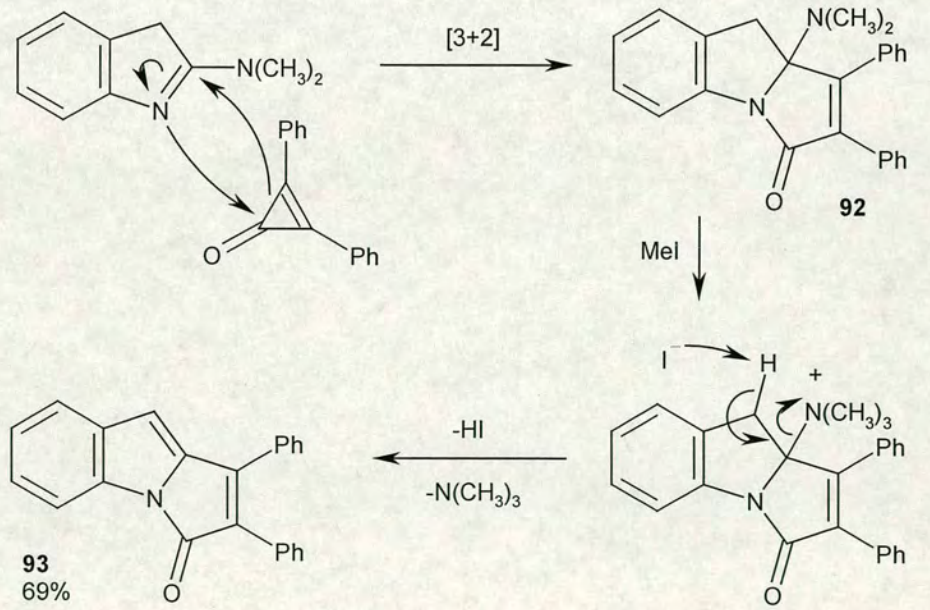
Reaction of 1-acetyl-3-indolinone with 1-cyano-2,2-bis(methylthio)acrylate in an excess of sodium hydride at room temperature leads directly to the benzopyrrolizinone **90** (Scheme 14). This reaction is very similar to those in section 1.1.2.3.1 (Scheme 9) but the use of an excess of sodium hydride gives a one-step synthesis of the benzopyrrolizinone **90** as opposed to the two-step synthesis involving the indole 2-propenoate **63** obtained when using one equivalent of sodium hydride. The mechanism most probably involves generation of the enolate anion **91** and nucleophilic displacement of a methylthio group followed by an addition-elimination ring-closure to form the amide.[17]



Scheme 14

1.1.2.5.2 Amide formation by cycloaddition

A [3+2] cycloaddition of (3*H*-indol-2-yl)-dimethylamine to diphenylcyclopropenone initiated by the attack of the indolyl nitrogen lone pair on the diphenylcyclopropenone carbonyl carbon gives the tricycle **92**. A Hoffmann elimination with methyl iodide affords the 1,2-diphenylpyrrolo[1,2-*a*]indol-3-one **93** (Scheme 15).[25]



Scheme 15

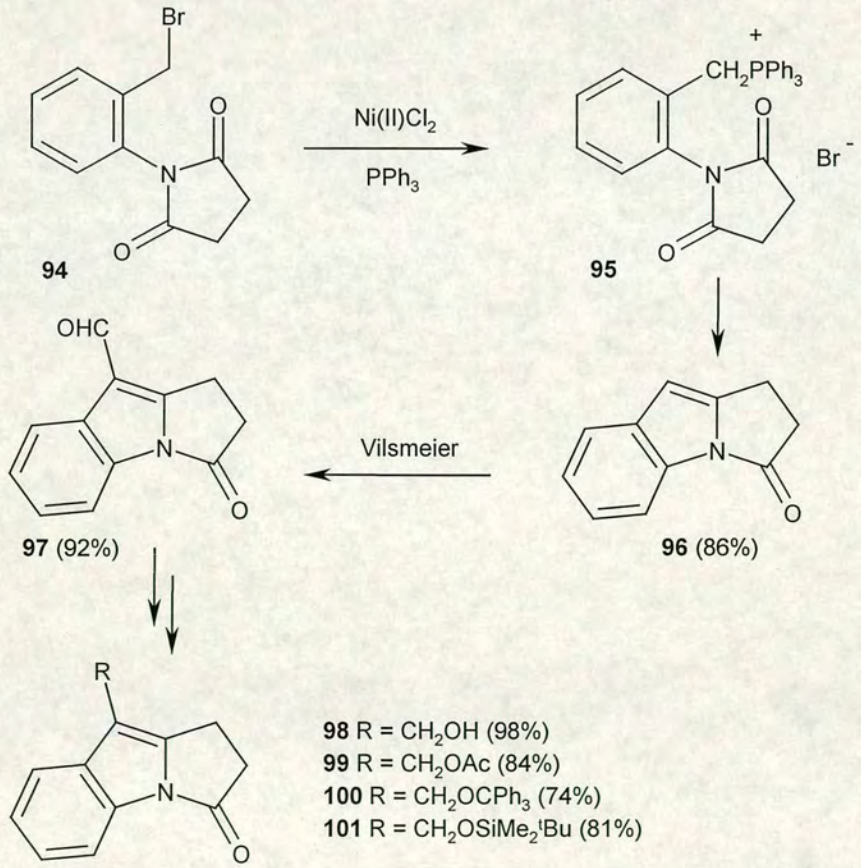
1.1.2.6 Formation by dehydrogenation of the 1,2-bond

Several reported syntheses of benzopyrrolizinones involve an initial ring-closure to give 1,2-dihydrobenzopyrrolizinones followed by dehydrogenation of the 1,2-bond to generate the enone moiety.

1.1.2.6.1 Ring-closure by 9,9a-bond formation

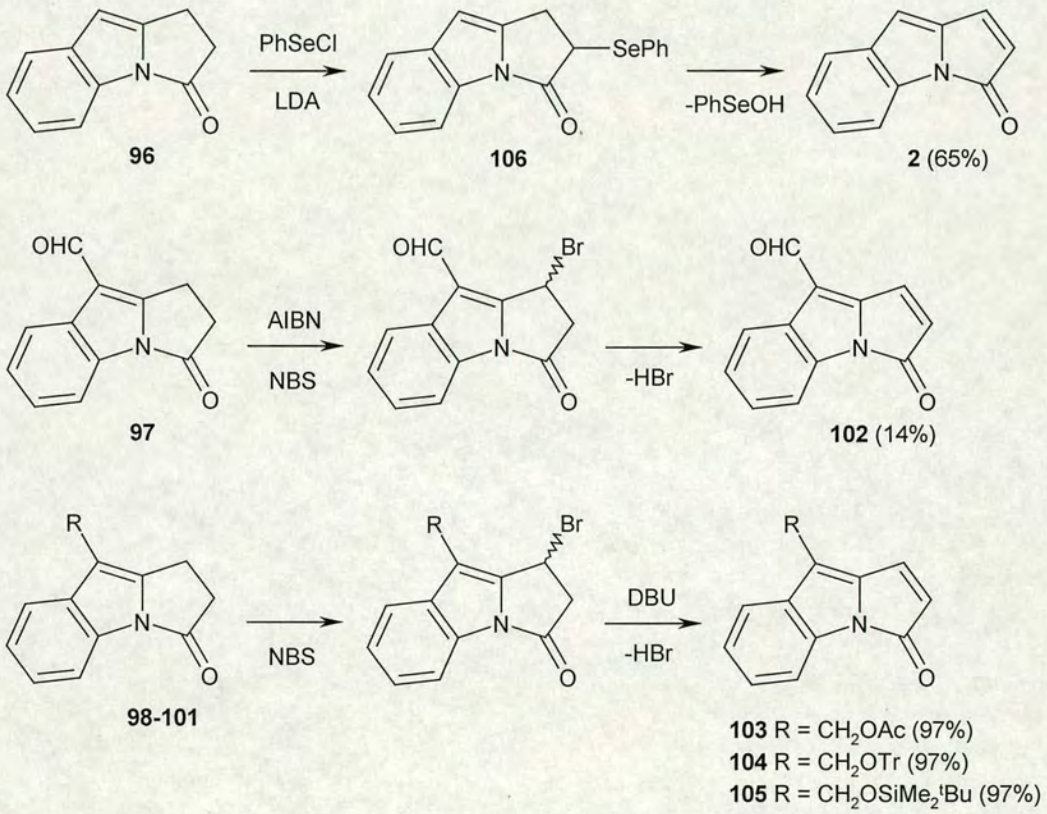
Flitsch and co-workers obtained a series of benzopyrrolizin-3-ones **2,102-105** from the 1,2-dihydro derivatives using several different reduction methods.[26]

When *N*-(2-bromomethylphenyl)succinimide **94** is treated with a catalytic amount of nickel(II)chloride and triphenylphosphine the resulting phosphonium bromide **95** cyclises by intramolecular Wittig olefination giving the parent 1,2-dihydro-benzopyrrolizinone **96**. Subsequent Vilsmeier formylation at the 9-position allows a range of derivatives to be synthesised **97-101** (Scheme 16).[27]



Scheme 16

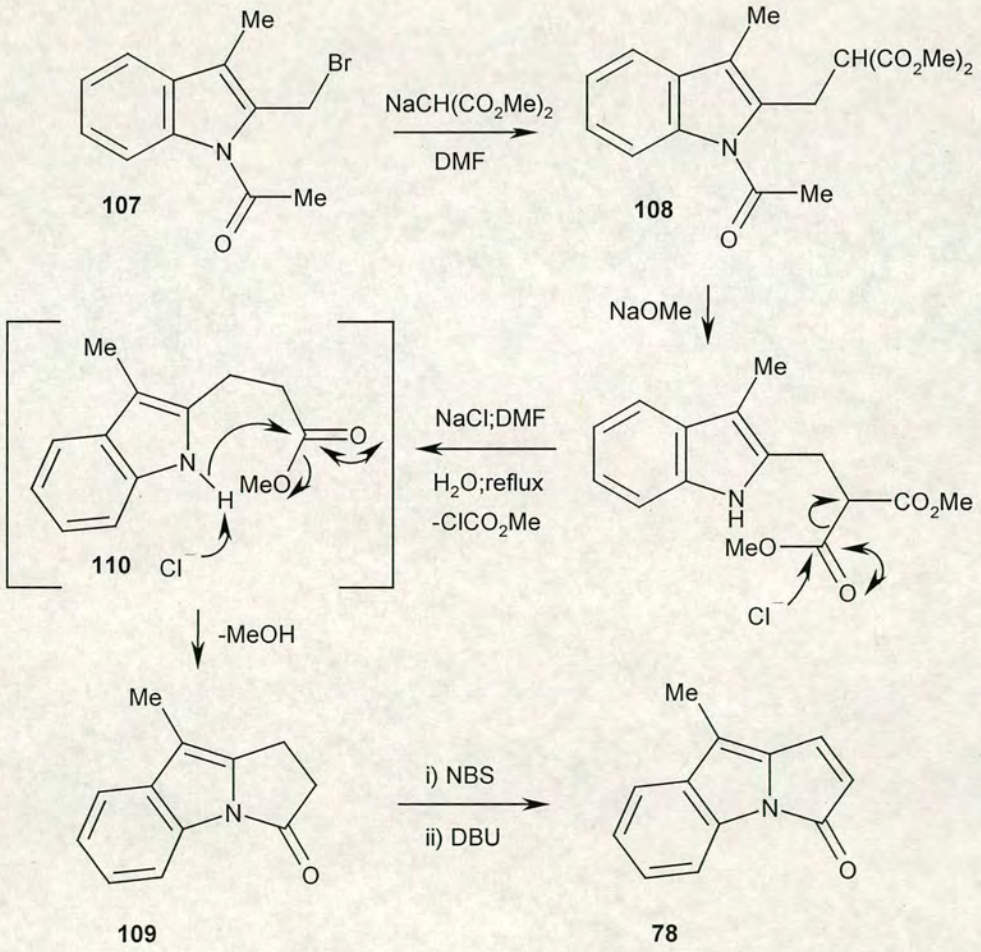
Several sets of reaction conditions can be used to effect dehydrogention of the 1,2-dihydro system. LDA and phenyl selenenyl chloride affords **106** which undergoes oxidative elimination of benzeneselenenic acid to generate **2** whilst 9-formyl-benzopyrrolizin-3-one **102** is formed with limited success by bromination of its 1,2-dihydro derivative **97** with NBS in the presence of azoisobutyronitrile. More successful dehydrogenations of the 1,2-dihydro derivatives **98-101** are achieved using NBS to effect ionic bromination followed by DBU to facilitate hydrogen bromide elimination to the benzopyrrolizin-3-ones **103-105** in good yields (Scheme 17).[26]



Scheme 17

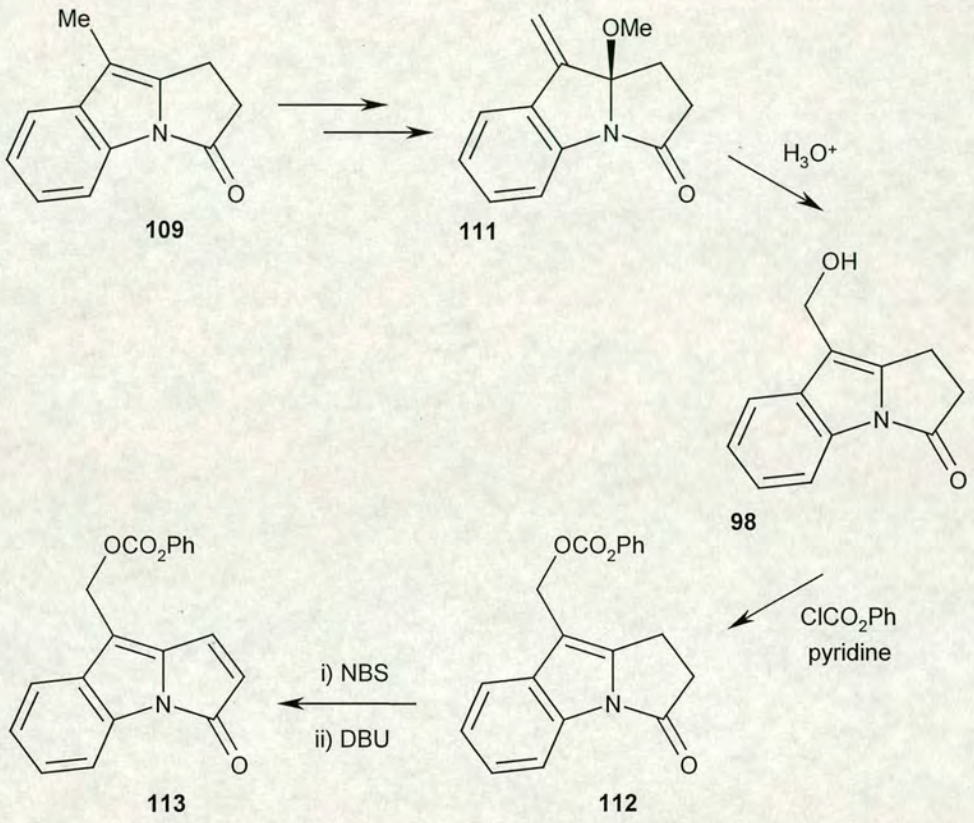
1.1.2.6.2 Ring-closure by 1,2-bond formation

N-Acetyl-2,3-dimethylindole reacts with molecular bromine to give the bromide **107** that readily undergoes nucleophilic substitution to afford the C-2 alkylated product **108**. Deacylation with sodium methoxide and subsequent treatment using Krapcho reaction conditions ($NaCl/H_2O/DMF$/reflux) effects ring-closure to **109**. Nucleophilic attack of the chloride ion on one of the ester groups generates a carbanion intermediate which is subsequently protonated by water to give **110**. Hydrolysis of the methyl chloroformate side-product regenerates the chloride ion and liberates carbon dioxide and methanol. Chloride ion attack deprotonates the pyrrole nitrogen atom driving cyclisation to the lactam **109** via loss of methanol.[28] Dehydrogenation with equivalent amounts of NBS then DBU gives 9-methyl-pyrrolo[1,2-*a*]indol-3-one **78** in 98% yield from the lactam (Scheme 18).[29]



Scheme 18

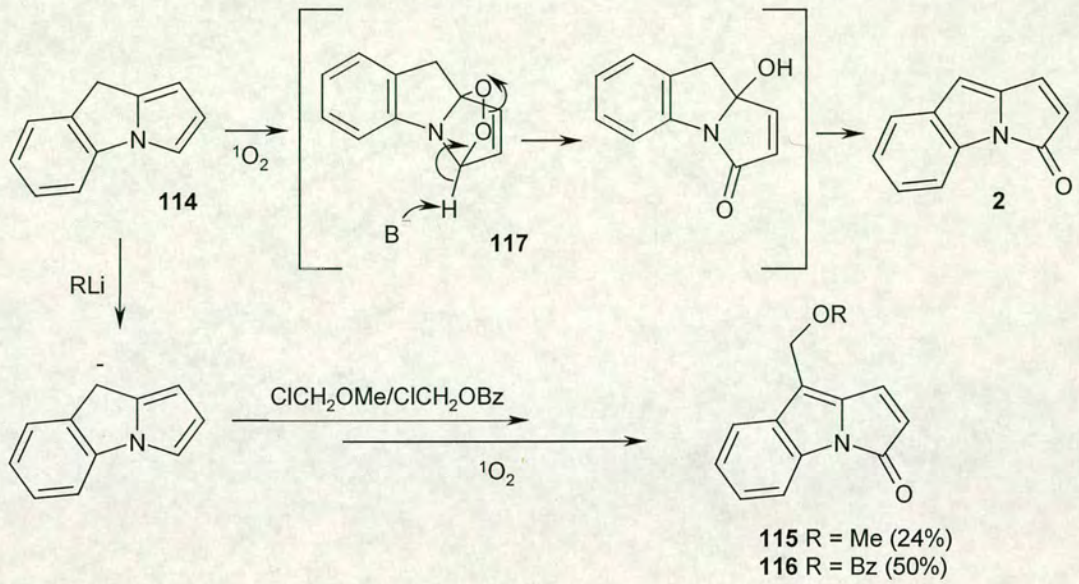
Functional group interconversion of the 9-substituent in the 1,2-dihydro system has also been demonstrated. Conversion of the lactam **109** to **111** (no experimental details are given by the authors), treatment with water followed by reaction with phenyl chloroformate and dehydrogenation with NBS/DBU affords the benzopyrrolizin-3-one **113** (Scheme 19).[29]



Scheme 19

1.1.2.7 Photooxidation

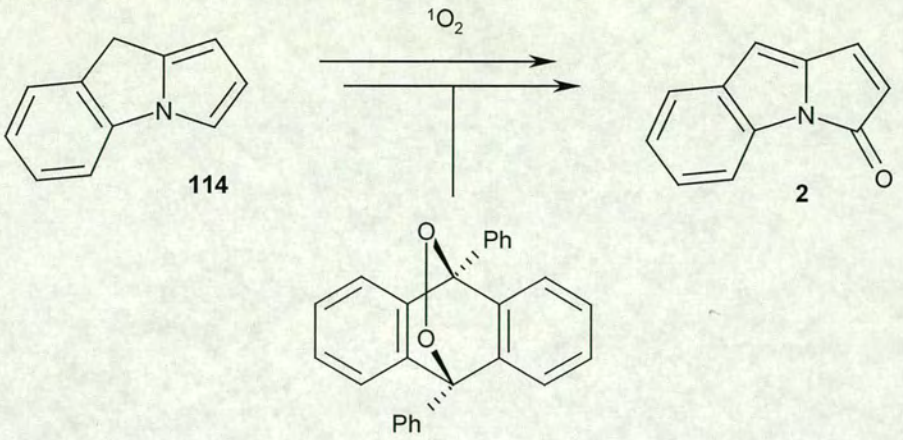
In the early 1970s Franck and co-workers utilised photooxidation as a route to benzopyrrolizin-3-ones. Photooxidation with singlet oxygen of 9*H*-pyrrolo[1,2-*a*]indole **114** in the presence of pyridine gave a 72% yield of the parent benzopyrrolizin-3-one **2**. [30,31] In similar reactions lithium derivatives of the tricycle **114** were alkylated using chloromethyl methyl ether and chloromethyl benzyl ether then crude the mixtures photooxygenated to afford the 9-alkylated products **115** and **116** (Scheme 20).[32]



Scheme 20

Pyridine was found to be necessary since it catalyses the ring-opening of the *endo*-peroxide intermediate **117**. A control reaction performed without pyridine was largely unsuccessful with only low a yield of product **2** (16%).

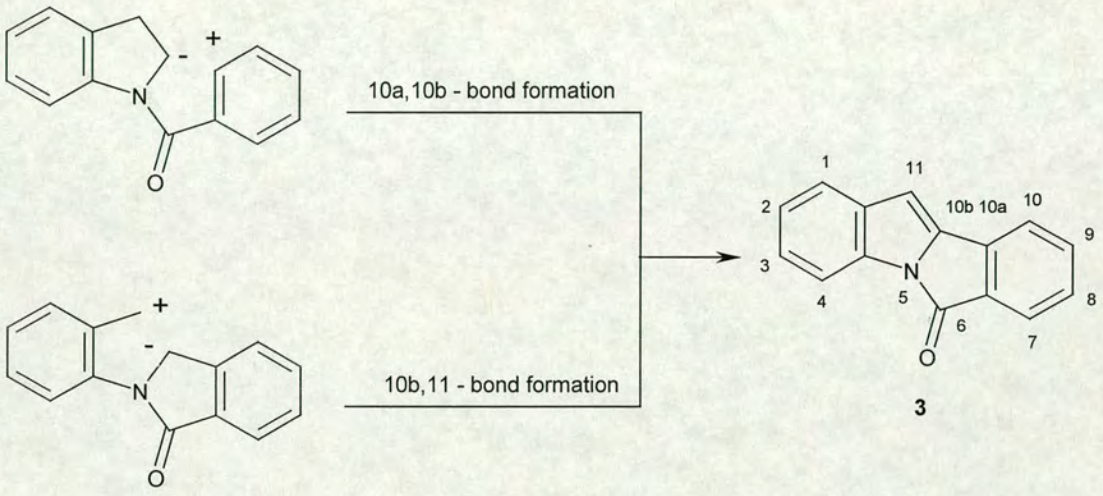
Two other oxygenation methods have been attempted. The first method of oxygenation of tricycle **114** was using hydrogen peroxide and sodium hypochlorite in DMF solution. On work-up only 2% of the parent compound **2** was isolated. In the second method tricycle **114** was oxygenated with singlet oxygen obtained by thermal decomposition of 9,10-diphenylanthracene *endo*-peroxide but again only 11% yield of the parent **2** was obtained after work-up (Scheme 21).[31]



Scheme 21

1.1.3 Isoindolo[2,1-*a*]indol-6-one synthesis

In the synthesis of isoindolo[2,1-*a*]indol-6-ones the ring-closure is generally by the formation of one of two bonds, the pyrrolone 10a,10b bond or the pyrrole 10b,11 bond (Scheme 22).



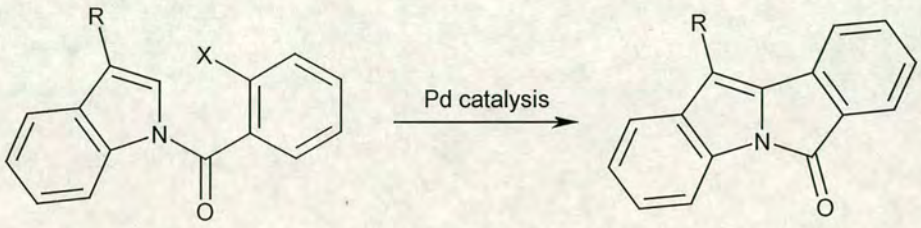
Scheme 22

The most common ring-closure is that forming pyrrolone 10a,10b bond and has been achieved by radical/photocyclisation and various palladium based catalysis reactions of 1-aroylindoles, whereas the less common pyrrole 10b,11 ring-closure involves cyclisation of *N*-alkylphthalimides.

1.1.3.1 10a,10b – Bond formation

1.1.3.1.1 Bond formation by palladium catalysis

In 1979, Itahara showed that 1-benzoylindole gives isoindolo[2,1-*a*]indol-6-one **3** *via* a Heck type reaction with palladium acetate in hot acetic acid.[33] The use of 2-iodo- and 2-bromo-benzoylindoles and improved catalytic systems have since facilitated increased yields of the parent tetracycle and some 11-substituted examples (Scheme 23).[34,33,36]



R	X	Product	Yield (%)	Catalytic system
H	H	**3**	47	$Pd(II)(OAc)_2$ (0.5 equiv), acetic acid, 110 °C, N_2, 15 h.
H	I	**3**	80	10 mol % $Pd(II)(OAc)_2$, 20 mol % PPh_3, TEAC (1 mol), K_2CO_3 (2 mol), CH_3CN, 12 h, reflux.
Me	I	**118**	63	10 mol % $Pd(II)(OAc)_2$, 20 mol % PPh_3, TEAC (1 mol), K_2CO_3 (2 mol), CH_3CN, 12 h, reflux.
H	Br	**3**	72	$Pd(0)(PPh_3)_4$, KOAc, DMA, 130 °C, 36 h.
CHO	Br	**119**	48	$Pd[CH_3CN]Cl_2$, TBAC, NaOCHO, DMF, 90 °C.
CHO	I	**119**	70	$Pd[CH_3CN]Cl_2$, TBAC, NaOCHO, DMF, 90 °C.

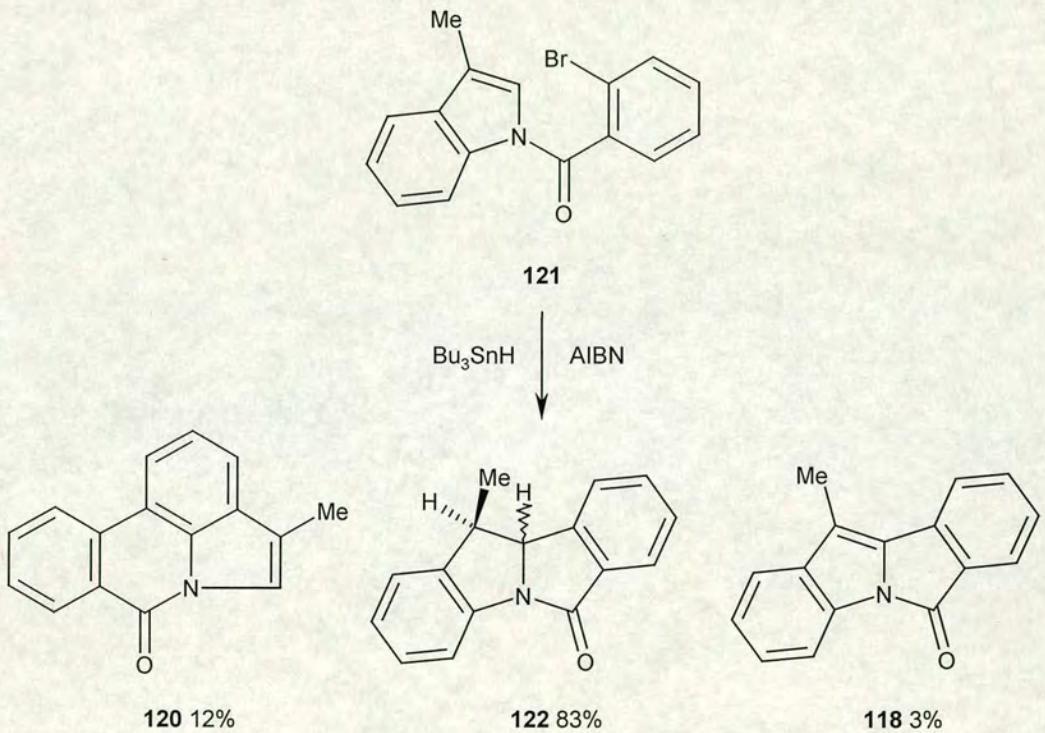
Scheme 23

1.1.3.1.2 Bond formation by radicals

Radical reactions of 1-aroylindoles have been shown to generate to isoindolo[2,1-*a*]indol-6-ones. However, neither solution phase radical cyclisation or photocyclisation are particularly effective in tetracycle formation.

1.1.3.1.3 Solution phase radical cyclisation

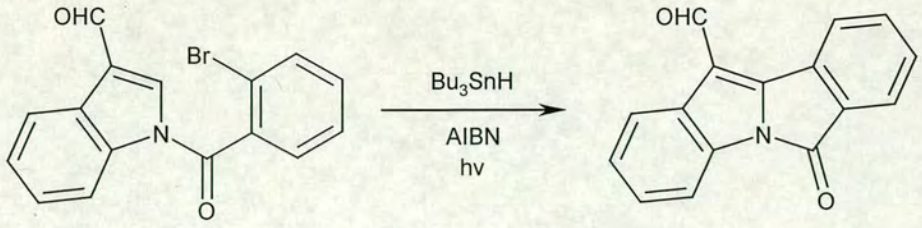
Whilst attempting to synthesise the 1,7-fused pyrrolophenanthridone **120**, Tsuge and co-workers found that the treatment of 1-(2-bromobenzoyl)-3-methylindole **121** with tributyltin hydride in the presence of azobisisobutyronitrile in boiling benzene gives 10b,11-dihydro-11-methylisoindolo[2,1-*a*]indol-6-one **122** in 83% yield. Also identified in the reaction products was 3% of 11-methyl-isoindolo[2,1-*a*]indol-6-one **118** that the authors suggest is formed *via* intramolecular abstraction of the indole C-2 proton by the benzoyl radical followed by radical cyclisation at the indole C-2 position and loss of a hydrogen atom to restore the aromaticity of the benzene ring to afford the product (Scheme 24).[37]



Scheme 24

1.1.3.1.4 Photocyclisation

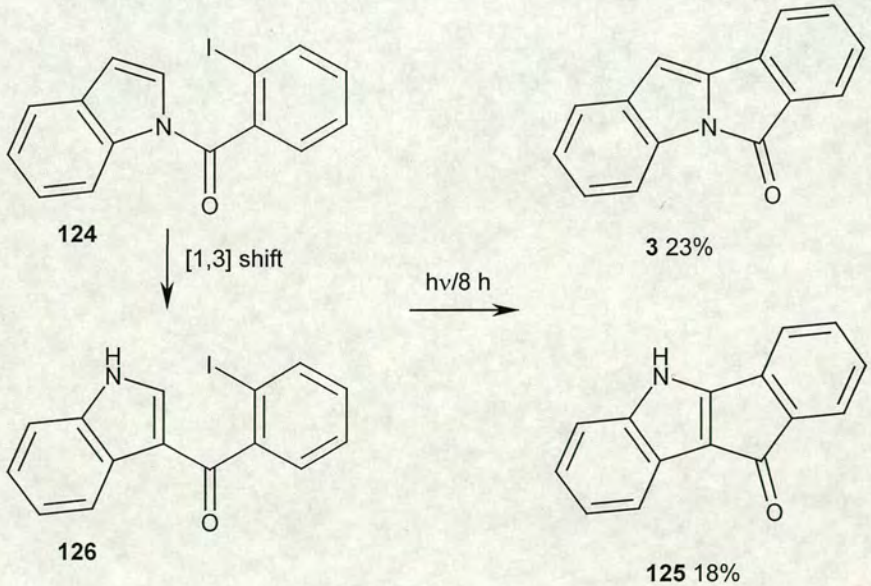
Irradiation of *N*-(2-bromobenzoyl)indole-3-carboxaldehyde **123** in benzene with tributyltin hydride and azobisisobutyronitrile as radical initiator affords the 11-formyl tetracycle **119** in 35% yield (Scheme 25).[36]



123 **119** 35%

Scheme 25

High-pressure mercury lamp irradiation of 1-(2-iodobenzoyl)indole **124** induces radical photocyclisation to isoindolo[2,1-*a*]indol-6-one **3**, in 23% yield. A second product, indeno[1,2-*b*]indol-10-one **125**, does not result from a rearrangement of isoindoloindol-6-one **3** but instead results from an initial migration of the benzoyl group of 1-(2-iodobenzoyl)indole **124** from C-1 to C-3 generating 3-(2-iodobenzoyl)indole **126**.[39] Such migration are well known under photolysis conditions.[38] Cyclisation follows, as in the generation of **3**, to afford **125** (Scheme 26).



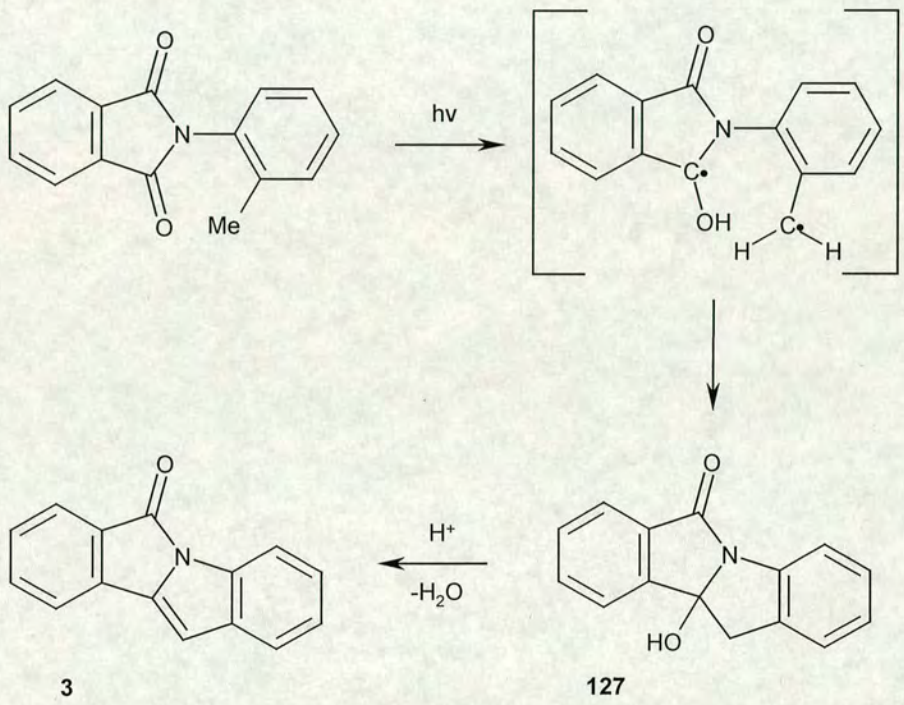
124 **126** **3** 23% **125** 18%

Scheme 26

1.1.3.2 10b,11 – Bond Formation

1.1.3.2.1 Photocyclisation

Irradiation of *N*-alkylphthalimides in alcohol with a high pressure mercury lamp affords the 10b,11-dihydrotetracycle **127** *via* intramolecular abstraction of a proton from the methyl group by the excited amide carbonyl (Scheme 27). Treatment with acid gives dehydrated tetracycle **3**.[40]

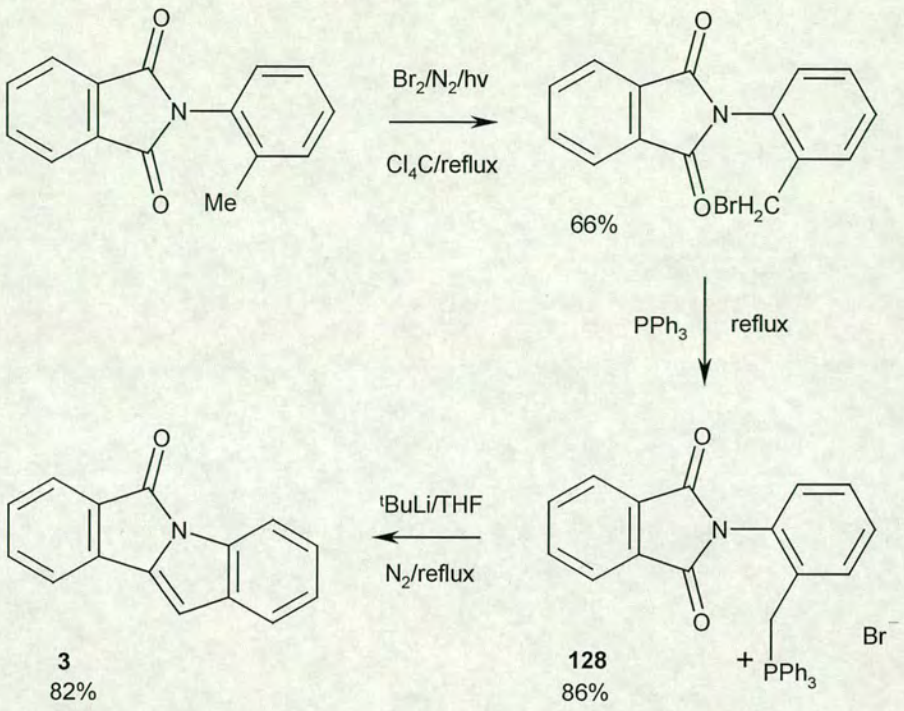


3 **127**

Scheme 27

1.1.3.2.2 Intramolecular Wittig reaction

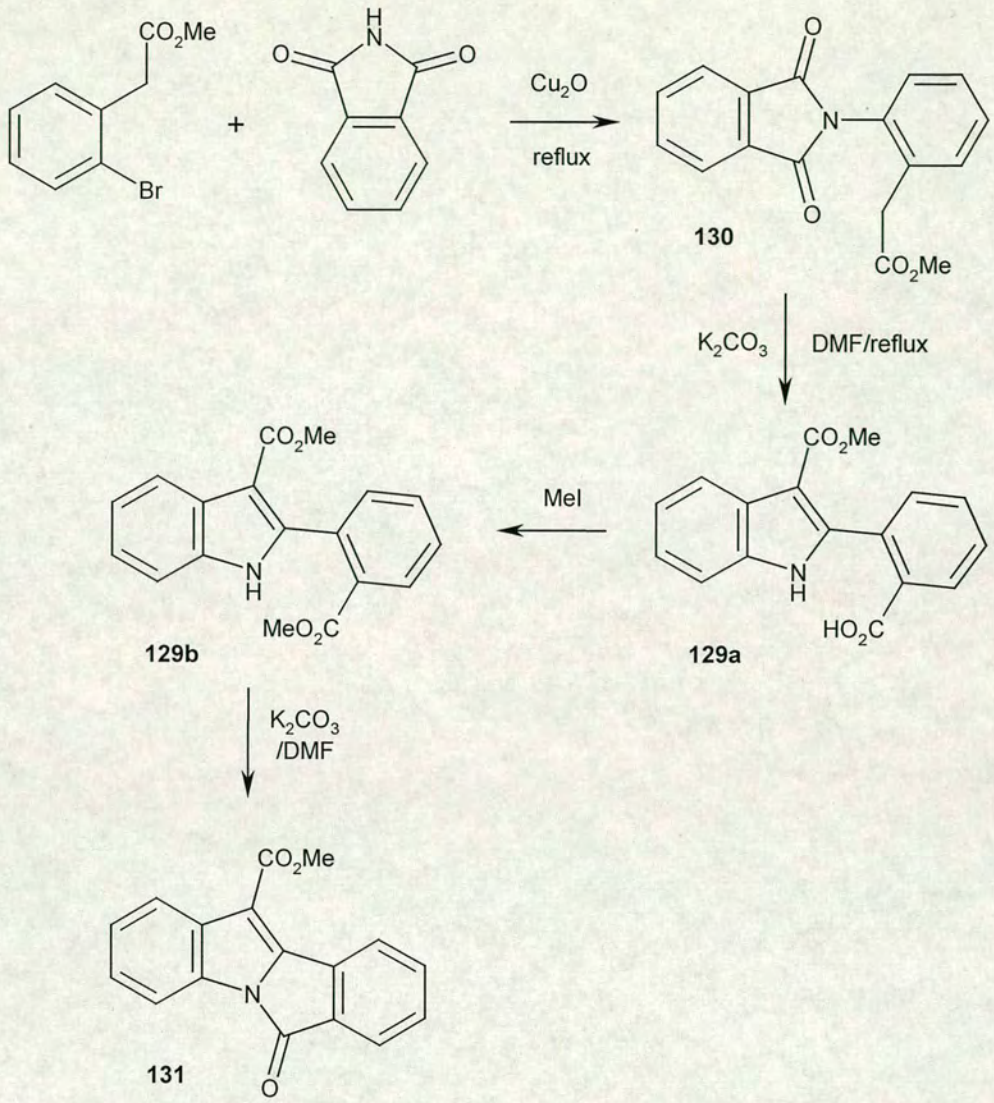
Zimmer and Crenshaw have also obtained the parent tetracycle **3** from *N*-(2-tolyl)phthalimide but *via* an intramolecular Wittig reaction (Scheme 28). Bromination of the tolyl group followed by treatment with triphenylphosphine under reflux affords the phosphonium salt **128**. Ring-closure is achieved with *t*-butyl lithium in good yield (82%).[41] An analogous synthesis used the Horner-Emmons variant of the Wittig reaction but gave only 25% ring-closure of the phosphonate.[41]



Scheme 28

1.1.3.2.3 Base facilitated bond formation

Despite the poor reaction of methyl 2-bromophenylacetate with phthalimide, even under harsh conditions, efficient indole **129a** formation (89%) from methyl 2-(*N*-phthalimide)phenylacetate **130** can be achieved by the use of potassium carbonate. Quantitative ring-closure of the indole **129a** by esterification of the carboxylic acid with methyl iodide to afford **129b** and treatment with a second equivalent of potassium carbonate gives the 11-methoxycarbonyl tetracycle **131** (Scheme 29).[42]


CO2Me
Br
+
H
N
O
O
Cu2O
reflux
O
N
O
130
CO2Me
K2CO3
DMF/reflux
CO2Me
N
H
HO2C
129a
MeI
CO2Me
N
H
MeO2C
129b
K2CO3
/DMF
CO2Me
N
O
131

Scheme 29

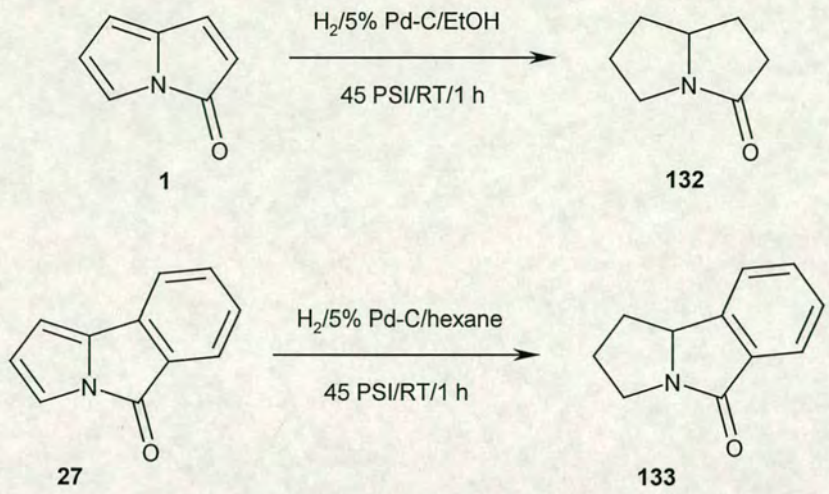
1.2 Chemical properties

This section aims to update new pyrrolizin-3-one **1** chemistry since the last review in 1994 and to review all known examples of benzopyrrolizin-3-one **2** and isoindoloindol-6-one **3** chemistry.[01] Pyrrolizin-3-ones have become more accessible and so more detailed studies into the reactivity of the ring system have been possible.[04] Relatively little comparative data is available for the benzopyrrolizin-3-one and isoindoloindol-6-one ring systems.

1.2.1 Reduction by hydrogenation

Pyrrolizin-3-one **1** and some 1- and 7-substituted pyrrolizin-3-ones have been hydrogenated, generally under mild conditions. Likewise pyrroloisoindol-5-one **27** and benzopyrrolizin-3-one **3** have also been treated under similar conditions. No high pressure hydrogenations have been documented in the literature to date (see discussion section 2.4.1).

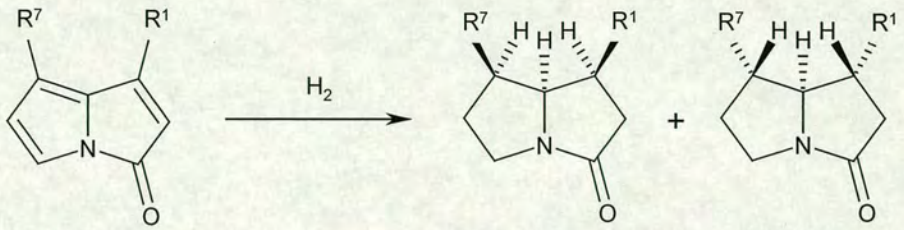
Hydrogenation of the pyrrolizin-3-one 1,2-double bond under mild conditions (5% Pd-C in ethanol at room temperature over 1 h at atmospheric pressure) has been previously demonstrated.[43] However, complete saturation of pyrrolizin-3-one **1** can be achieved under the slightly more forcing conditions of 5% Pd-C in ethanol at room temperature over 2 h at 45 PSI (Scheme 30).[44] Hydrogenation of pyrroloisoindol-5-one **27** using 5% Pd-C in hexane at room temperature over 2 h at 45 PSI affords the 1,2,3,9b-tetrahydropyrroloisoindol-5-one **133** in 90% yield (Scheme 30).[45]



Scheme 30

Hydrogenations of 1- and 7-monosubstituted pyrrolizin-3-ones have also been performed and complete reduction generally results in the formation of two diastereoisomers (Scheme 31).[44]

The *cis*-diastereoisomer, where the ring-junction proton is *cis* with respect to the adjacent methine protons, predominates over the *trans*-diastereoisomer (Table 3). In the case of 1-substituted pyrrolizinones the diastereoselectivity is likely to be a consequence of the formation of the 1,2-dihydro species *en route* to the perhydro system. Steric hindrance generated by the methyl group on one face of the 1,2-dihydro intermediate leads to a predominance of the *cis*-diastereoisomer by virtue of dihydrogen addition occurring selectively on the less hindered face. However, in the 7-substituted pyrrolizinones the high diastereoselectivity results from the *cis*-hydrogenation mechanism of the pyrrole ring leading to the hydrogen atoms at C-7 and C-7*a* being *cis* to one another. The degree of diastereoselective control is most greatly governed by choice of catalyst although solvent choice also has an effect to a lesser extent. However, there are no clear rules for catalyst or solvent selection.



7,11,13,16 **134-137** **138-141**

R^1=H, R^7≠H

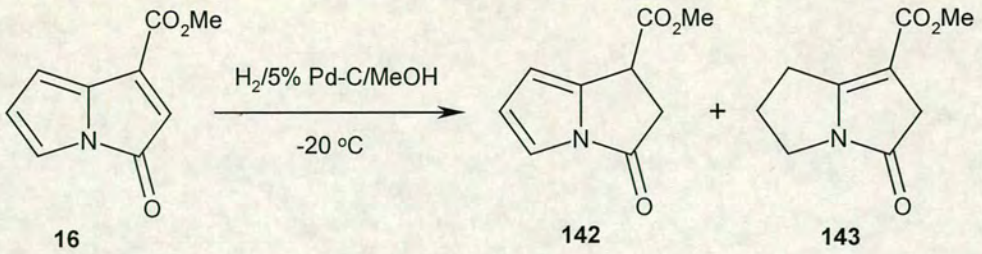
R^1≠H, R^7=H

Scheme 31

Pyrrolizinone	Substituent	Catalyst	Solvent	Pyrrolizidinone		Diastereo. ratio
				cis	*trans*	*cis*:*trans*
7	1-Me	Raney Ni	EtOAc	**134**	**138**	95:5
16	1-CO_2Me	Pd-C	MeOH	**135**	**139**	99:1
11	7-Me	Rh-C	EtOAc	**136**	**140**	98:2
13	7-CO_2Me	Rh-Al_2O_3	AcOH	**137**	**141**	100:0

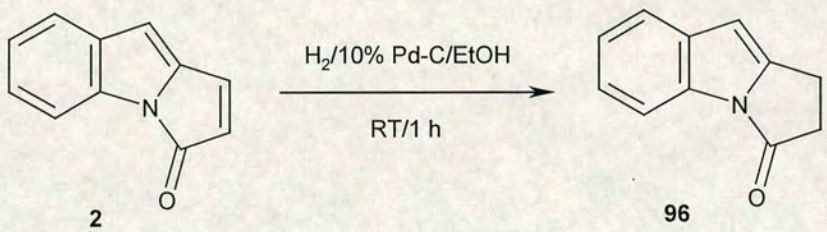
Table 3 – Hydrogenation product of 1- and 7-monosubstituted pyrrolizin-3-ones

1-Methoxycarbonylpyrrolizin-3-one **16** is unstable at room temperature and so an initial hydrogenation performed at –20 °C at atmospheric pressure is required to obtain stable 1,2-dihydropyrrolizinone **142** and 2,5,6,7-tetrahydropyrrolizinone **143** derivatives (Scheme 32) that are subsequently hydrogenated at room temperature at 55 PSI to afford the completely reduced pyrrolizidin-3-ones **135** and **139**.



Scheme 32

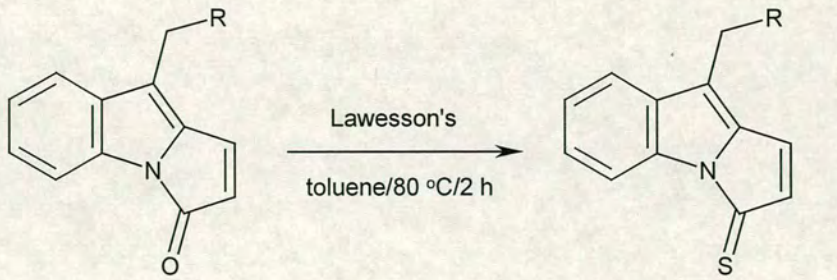
Only one example of benzopyrrolizin-3-one **2** hydrogenation has been reported in which the corresponding 1,2-dihydrobenzopyrrolizin-3-one **96** is obtained in 92% yield under mild conditions using 10% Pd-C in ethanol (Scheme 33).[31]



Scheme 33

1.2.2 Thionation with Lawesson's reagent

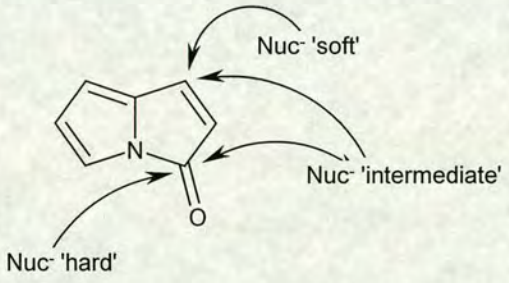
Flitsch and co-workers found that the treatment of the benzopyrrolizinones **104** and **105** with Lawesson's reagent gave selective reaction of the lactam carbonyl group to afford the benzopyrrolizine-3-thiones **144** and **145** respectively in good yields (Scheme 34).[26]



Scheme 34

1.2.3 Reactions with nucleophiles

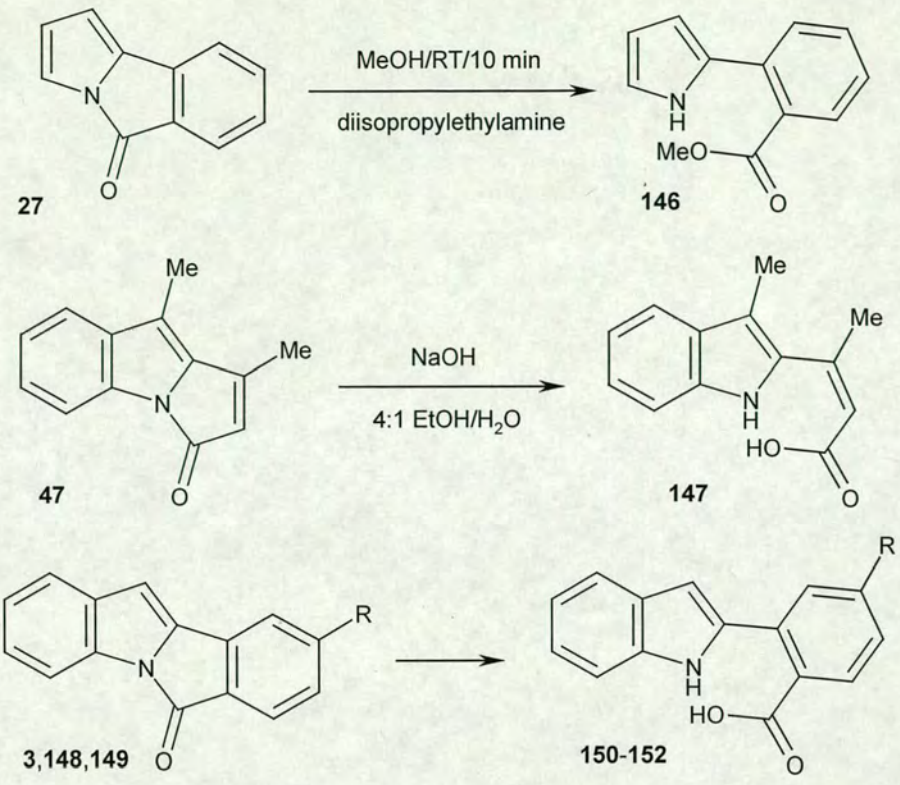
There is considerable scope for the reaction of nucleophiles with the pyrrolizin-3-one system **1** since it has both 'hard' and 'soft' electrophilic centres. 'Hard' nucleophiles may be expected to react at the 'hard' carbonyl carbon, whereas 'soft' nucleophiles may be expected to react at the 'soft' C-1 position. Nucleophiles of intermediate hard/softness may react at either electrophilic centre (Scheme 35). Whilst nucleophilic reactions with the pyrrolizin-3-one system **1** have been relatively well investigated, little such chemistry of either the benzopyrrolizinone **2** or isoindoloindolone **3** systems has been reported (see discussion section 2.4.3).



Scheme 35

1.2.3.1 Reactions with *O*-nucleophiles

Treatment of pyrrolizinones with 'hard' nucleophiles such as hydroxide or alkoxide ions results in ring-opening by cleavage of the amide linkage to generate (*Z*)-3-(pyrrol-2-yl)propenoic acids or the equivalent esters respectively.[01] Such ring-opening reactions have also been demonstrated for the pyrroloisoindolone, benzopyrrolizinone and isoindoloindolone systems. Pyrroloisoindol-5-one **27** undergoes complete ring-opening to the methyl ester **146** when treated with a catalytic quantity of diisopropylethylamine in methanol (Scheme 36).[45] 1,9-Dimethylbenzopyrrolizin-3-one **47** readily ring-opens upon treatment with sodium hydroxide in 4:1 ethanol/water to afford 2-propenoic acid **147**.[14] Similarly, the isoindoloindoles **3**,**148**,**149** also give the appropriate ring-opened acids **150-152** (Scheme 36, Table 4).[46,47] In all cases the 'hard' character of *O*-nucleophiles results solely in attack at the 'hard' carbonyl carbon causing cleavage of the amide bond and affording the ring-opened products.



Scheme 36

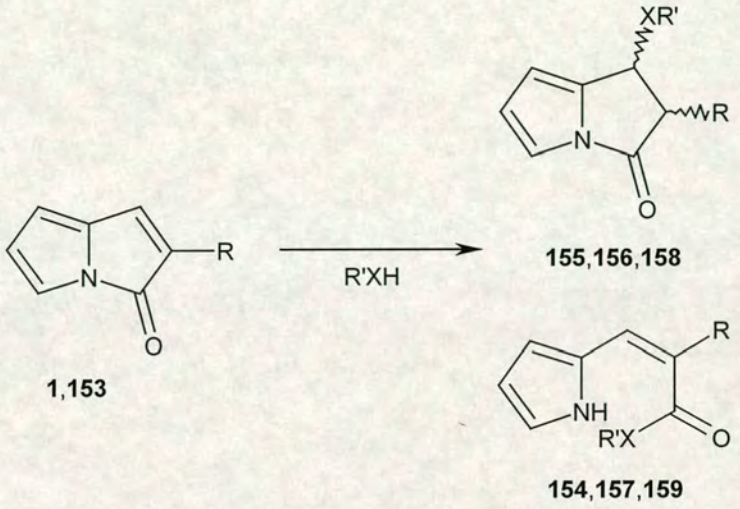
Isoindoloindole	R	Base	Solvent	Conditions	Product	Yield	Ref
3	H	NaOH	$MeOH/H_2O$	15 min/Δ	**150**	67%	**48**
3	H	^tBuOK	$^tBuOH/H_2O$	12 h/82 °C	**150**	75%	**49**
148	Me	^tBuOK	$^tBuOH/H_2O$	12 h/82 °C	**151**	74%	**49**
149	Cl	^tBuOK	$^tBuOH/H_2O$	12 h/82 °C	**152**	70%	**49**

Table 4 – Reagents, conditions and yield of ring-opening reactions with *O*-nucleophiles

1.2.3.2 Reactions with *N*-nucleophiles

The intermediate hardness of amines gives the potential for nucleophilic attack at either of electrophilic centres of pyrrolizin-3-one **1**. The addition of *t*-butylamine to pyrrolizin-3-one **1** in methanol at room temperature leads to entirely ring-opened propenamide **154** whereas the same reagents in acetone afford only the 'Michael' addition product **155** over 48 h. The use of piperidine as the amine reagent in

methanol gives only the 'Michael' addition product **156** but when used in acetone gives a 74:26 mixture of 'Michael' and ring-opened **157** products. The reduced reactivity of aniline is such that only the 'Michael' product **158** can be obtained, and even then under forcing conditions (Scheme 37, Table 5).[48]



Scheme 37

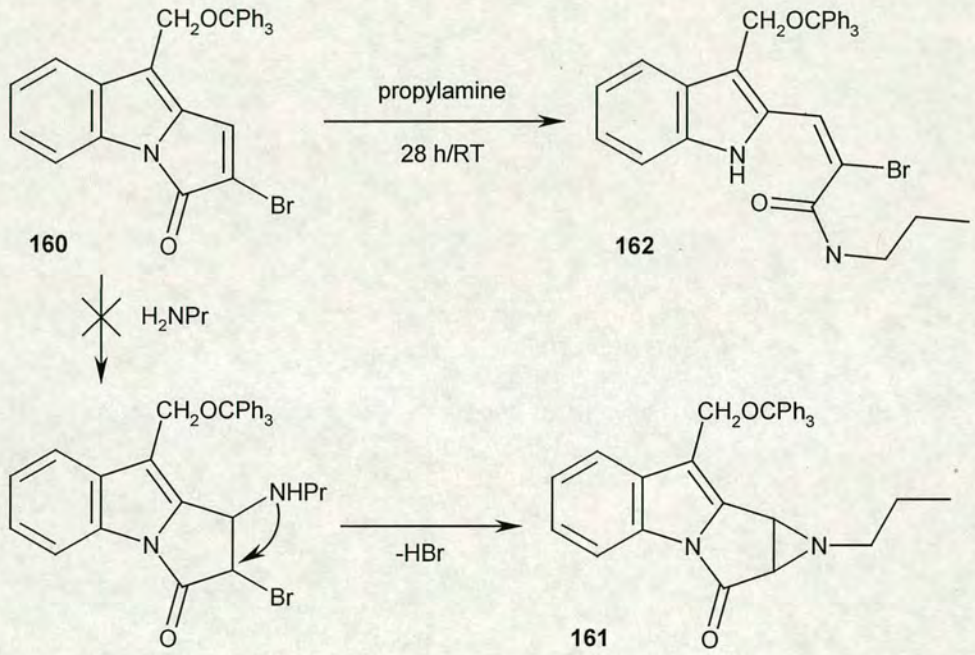
Pyrrolizinone	R	Amine R'	X	Conditions	Products	Ratio	Yield (%)
1	H	^{t}Bu	NH	MeOH/RT	**154** -	100:0	93
1	H	^{t}Bu	NH	acetone/RT	- **155**	0:100	61
1	H	$(CH_2)_5$	N	MeOH/RT	- **156**	0:100	91
1	H	$(CH_2)_5$	N	acetone/RT	**157** **156**	26:74	-
1	H	Ph	NH	H_2O/acetone/Δ	- **158**	0:100	68
153	Me	$(CH_2)_5$	N	acetone/RT	**159** -	100:0	79

Table 5 – Reagents, conditions and yield of ring-opening reactions with *N*-nucleophiles

A 2-position substituent greatly affects the selectivity of the nucleophilic attack. The addition of piperidine to 2-methylpyrrolizinone **153** in acetone afford solely the propenamide **159** in stark contrast to the 74:26 mixture of 'Michael' and ring-opened products observed for the same reaction with the parent pyrrolizinone **1** (Scheme 37).

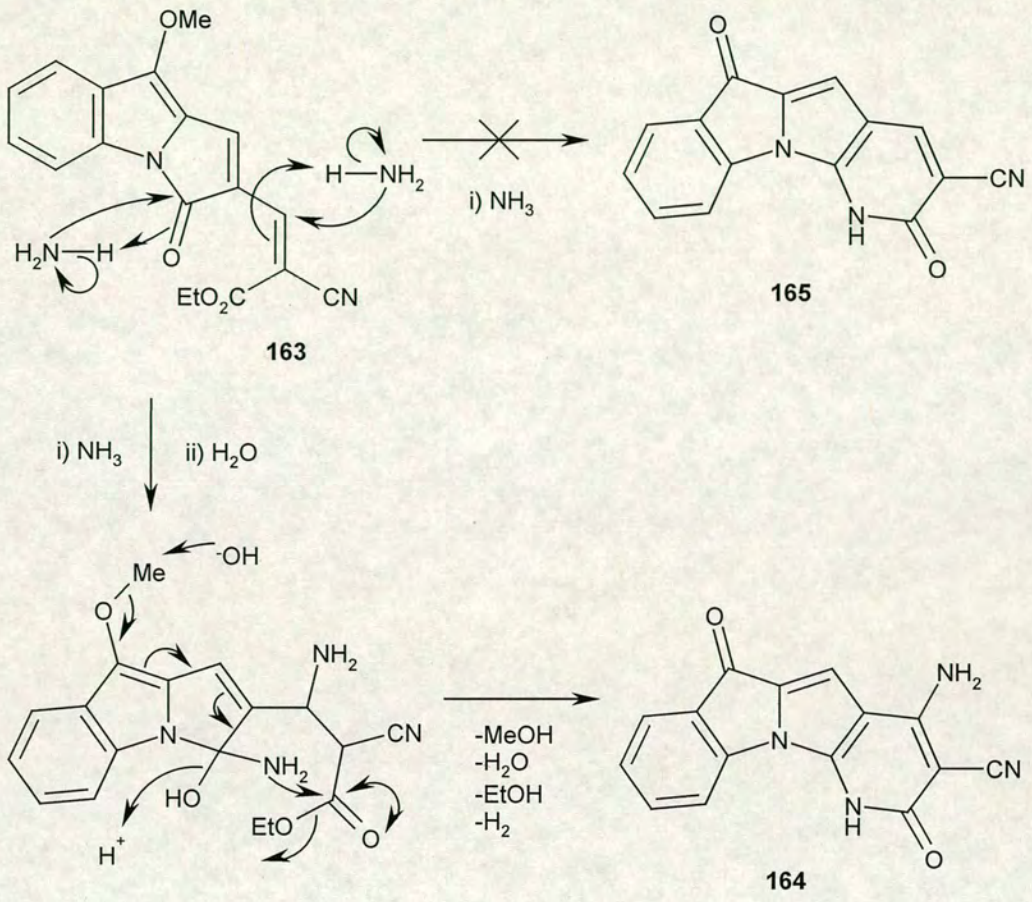
It is suggested that the difference in products is a result of the influence of the methyl substituent on the polarity of the enone double bond and therefore the relative hardness/softness of C-1.[48]

Only one example of an amine reacting with a benzopyrrolizinone has been described. Flitsch and co-workers intended that a 'Michael' addition of propylamine across the 1,2-double bond of 2-bromo-9-(triphenylmethoxy)methyl-benzopyrrolizin-3-one **160** followed by an intramolecular substitution and loss of hydrogen bromide would result in aziridine formation **161**. This did not occur and the ring-opened propenamide **162** was found to be the only product (Scheme 38).[26]



Scheme 38

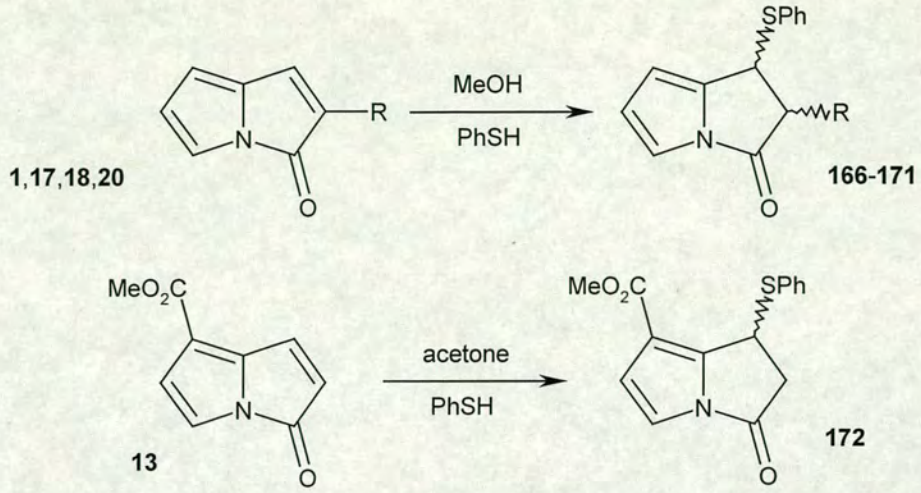
Tugusheva *et al* found, whilst attempting a cyclisation of the cyano ester derivative **163** by ammonolysis, that a second process involving ammonia addition gave the tetracycle **164** rather than **165** (Scheme 39). The authors offer no indication of the relative rates of the processes and hence it is not known whether attack by ammonia at the pyrrolone carbonyl carbon, amidation or ammonia addition at the 2-position of the acrylic ester occurs first.[49]



Scheme 39

1.2.3.3 Reactions with *S*-nucleophiles

Reactions of pyrrolizin-3-ones with thiophenol leads very quickly to only 'Michael' adducts since the 'soft' thiol group attacks the 'soft' enone β–carbon centre (Scheme 40). However, the ratio of *syn* and *anti* products varies widely (Table 6) and is probably dependent on the substituent present. Addition of thiophenol at C-1 of 7-methoxycarbonylpyrrolizinone **13** also affords solely 'Michael' adduct **172**.[44,48]

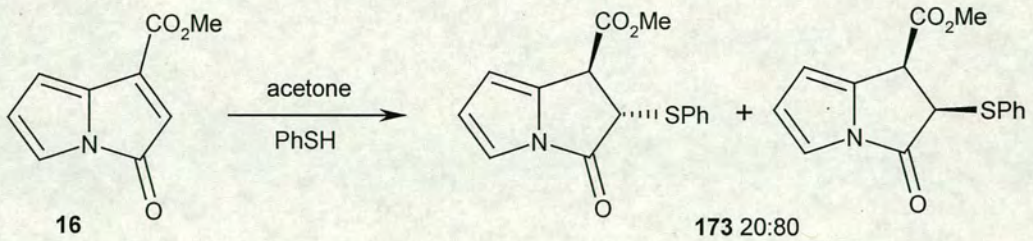


Scheme 40

Pyrrolizinone	R	Products	*syn*:*anti*
1	H	**166** -	100:0
17	Me	**167** **168**	92:8
18	CN	**169** **170**	35:65
20	CO_2Me	- **171**	0:100

Table 6 – Products of reactions of pyrrolizin-3-one with thiophenol

When thiophenol is added to 1-methoxycarbonylpyrrolizinone **16** the regioselectivity around the enone is reversed and addition of the thiol occurs at the 2-position to give an 80:20 *syn*:*anti* mixture of 'Michael' adducts **173** (Scheme 41).[44]



Scheme 41

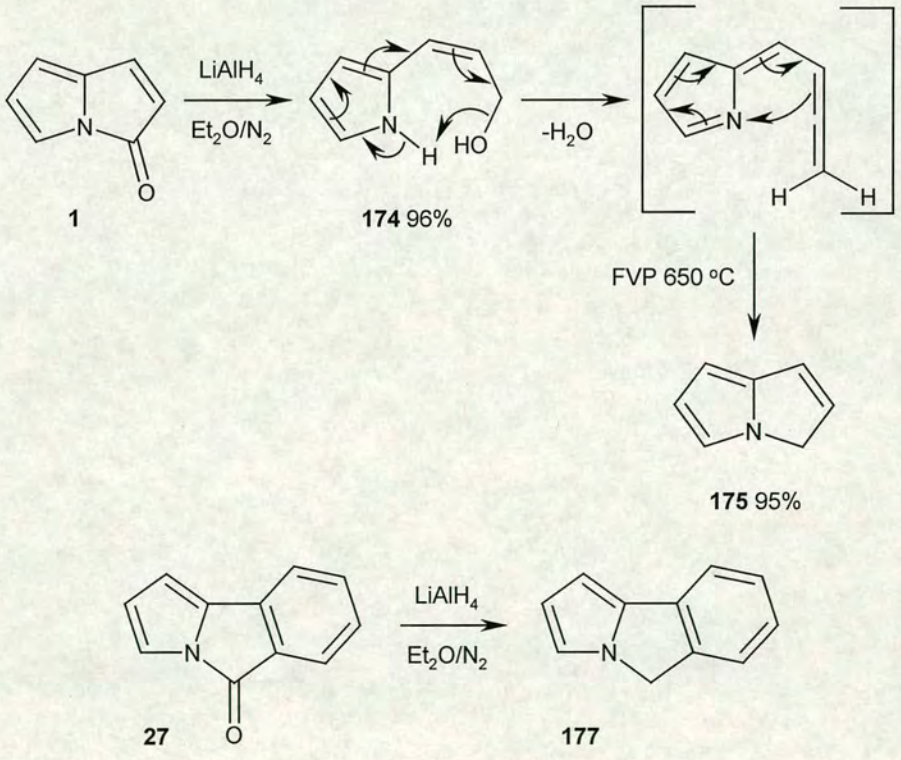
1.2.3.4 Reactions with *H*-nucleophiles

Pyrrolizin-3-one has been reacted with both lithium aluminium hydride ('hard') and sodium borohydride ('soft').

1.2.3.4.1 Reaction with lithium aluminium hydride

Pyrrolizin-3-one **1** is readily reduced by lithium aluminium hydride at –78 °C to afford exclusively the *Z*-configuration allylic alcohol **174** in high yield. Gas-phase pyrolysis of **174** in a fashion analogous to that of 2-propenoate esters (section 2.1.1), *via* elimination of water and electrocyclisation, generates 3*H*-pyrrolizine **175** (Scheme 42).[50]

Similarly, pyrroloisoindol-5-one **27** also reacts readily with lithium aluminium hydride to afford the ring-opened 2-arylpyrrole **176** (69% yield) and subsequent pyrolysis leads to the formation of 5*H*-pyrroloisoindole **177** in 94% yield.[50]

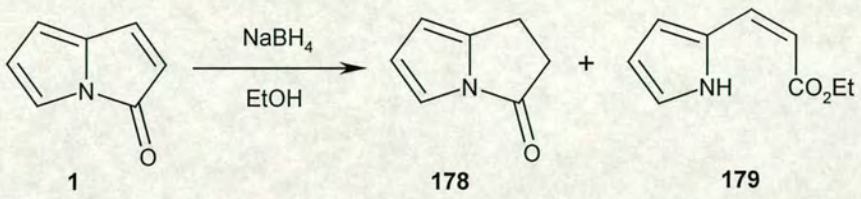


1 **174** 96% **175** 95% **27** **177**

Scheme 42

1.2.3.4.2 Reactions with sodium borohydride

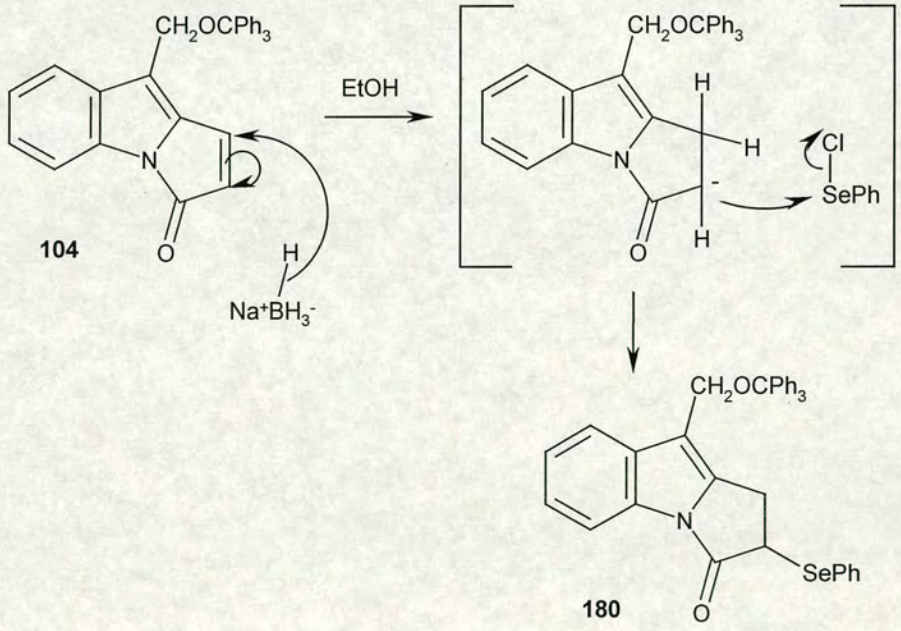
Treatment of pyrrolizin-3-one **1** with sodium borohydride in ethanol leads to 1,2-dihydropyrrolizin-3-one **178** and the ring-opened ethyl ester **179**, the latter a result of nucleophilic attack of an ethoxide anion at the carbonyl carbon (Scheme 43).[51] No experimental details were given regarding the reaction time or the ratio of reaction products.



1 **178** **179**

Scheme 43

Sodium borohydride has been used with phenyl selenenyl chloride to effect 1,2-bond reduction of the benzopyrrolizinone **104** to give 1,2-dihydro-2-phenylseleno-benzopyrrolizinone **180** in 40% yield (Scheme 44).[26]



104 **180**

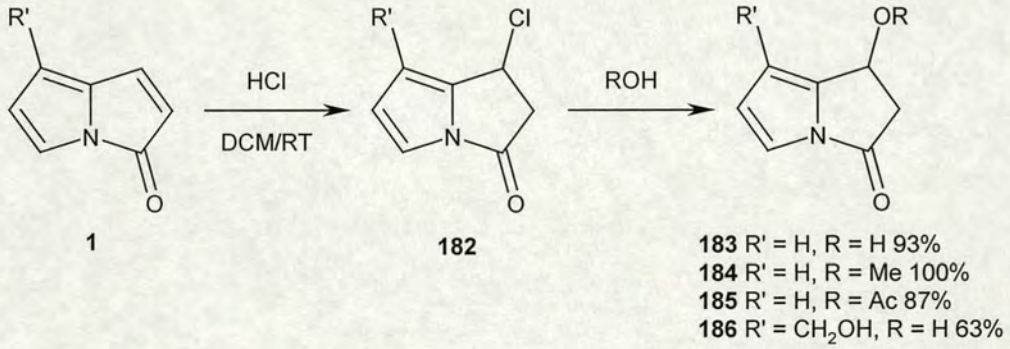
Scheme 44

1.2.4 Reactions with electrophiles

As in the reactions with nucleophiles the vast majority of reactions with electrophiles have been performed on pyrrolizin-3-ones whilst only one reported example concerns the benzopyrrolizin-3-one system.

1.2.4.1 Treatment with hydrogen chloride

Under acid conditions pyrrolizin-3-one **1** does not undergo ring-opening, as under basic conditions (section 3.2.1), to the pyrrol-2-ylpropenoate **181** as might be expected due to the presence of the lactam functionality. Instead, treatment of a dichloromethane solution of pyrrolizin-3-one **1** with hydrogen chloride gas gives 1-chloropyrrolizin-3-one **182** and subsequent quenching with *O*-nucleophiles such as sodium acetate (in acetic acid), methanol or water leads to rapid displacement of the labile chloro substituent and affords 1-acetoxy-, 1-methoxy- and 1-hydroxy-1,2-dihydropyrrolizin-3-ones **183-185**. This method provides a useful route to pyrrolizin-3-ones with an oxygen functionality in the 1-position and has been used as the key step in the synthesis of the alkaloid **186** (Scheme 45).[05]



1 **182**

183 R' = H, R = H 93%
184 R' = H, R = Me 100%
185 R' = H, R = Ac 87%
186 R' = CH_2OH, R = H 63%

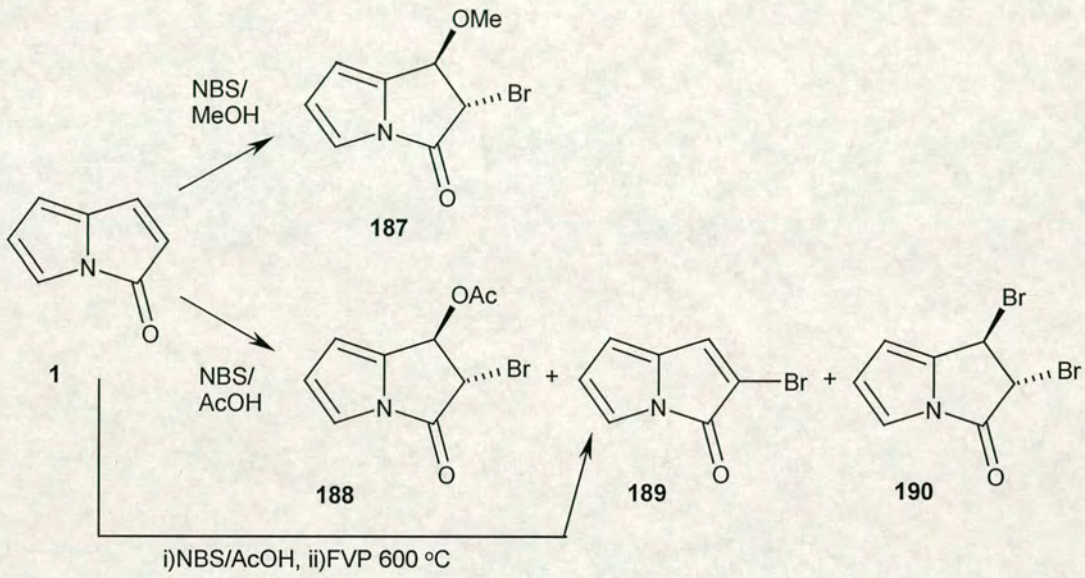
Scheme 45

1.2.4.2 Bromination reactions

Bromination of pyrrolizin-3-one **1** has been achieved by the use of *N*-bromosuccinimide (NBS) under several different conditions.

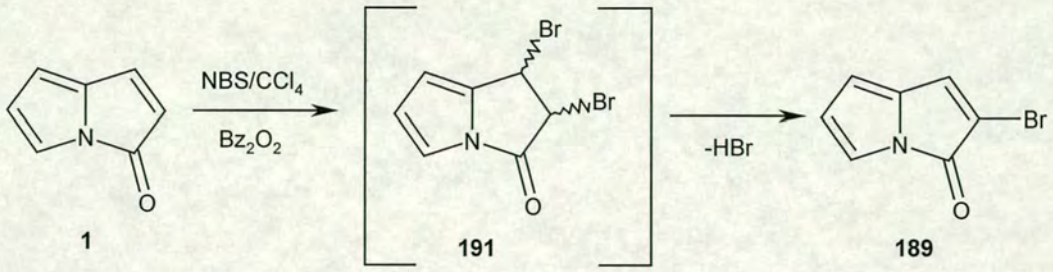
Treatment of pyrrolizin-3-one **1** in methanol with NBS affords the 1-methoxy-2-bromo-1,2-dihydropyrrolizinone **187** whereas treatment in glacial acetic acid leads to

a mixture of products comprising 1-acetoxy-2-bromo-1,2-dihydropyrrolizinone **188**, 2-bromo-1,2-dihydropyrrolizinone **189** and 1,2-dibromo-1,2-dihydropyrrolizinone **190**. However, complete elimination of acetic acid from the crude reaction mixture can be achieved under FVP conditions to afford 2-bromopyrrolizinone **189** as the sole product (Scheme 46).[52]



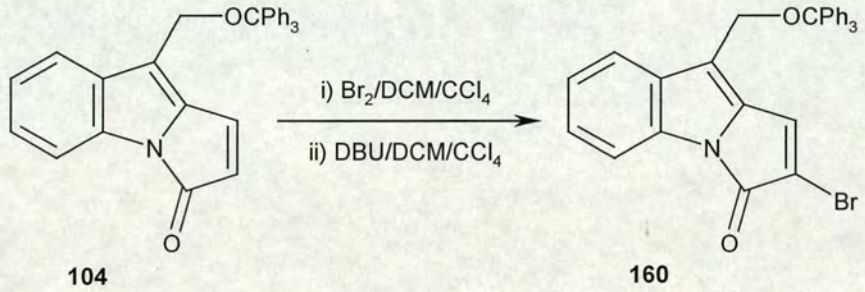
Scheme 46

Under free radical conditions, using NBS in carbon tetrachloride with dibenzoyl peroxide as an initiator, the only product isolated from the reaction of pyrrolizin-3-one **1** was 2-bromopyrrolizinone **189** (55% yield). No 1,2-dibromopyrrolizinone **191** was obtained as may be expected using such reaction conditions. The authors suggest that the product **189** is most probably formed by the initial formation of the dibromo compound followed by hydrogen bromide elimination (Scheme 47).[52]



Scheme 47

Whilst pyrrolizin-3-one **1** does not react with molecular bromine at room temperature[52], Flitsch has demonstrated that the reaction of 9-(triphenylmethoxy)methylbenzopyrrolizin-3-one **104** with bromine, initially at –30 °C in dichloromethane then warming to ambient temperature, and subsequent hydrogen bromide elimination with DBU gives the 2-bromo-9-(triphenylmethoxy)methylbenzopyrrolizin-3-one **160** in 45% yield (Scheme 48).[26]



Scheme 48

1.2.5 Pericyclic reactions

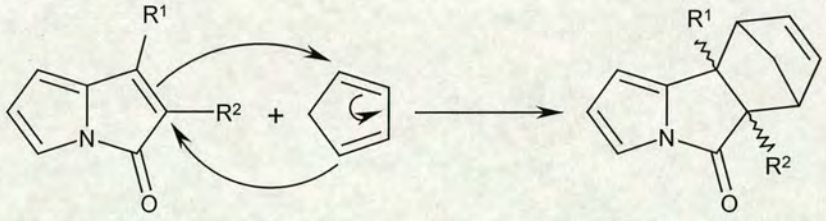
Pyrrolizin-3-one **1** comprises fused pyrrole and cyclopentenone rings and may be expected to have both diene and dienophilic character. While there are no examples of the pyrrole ring showing diene character, the cyclopentenone ring does show dienophile character and readily undergoes cycloaddition reactions. Cycloaddition reactions of the enone double bond in benzopyrrolizin-3-one system also occur (see discussion section 2.4.2).

1.2.5.1 Diels-Alder additions

Diels-Alder type reactions of pyrrolizin-3-ones with cyclopentadiene and with isobenzofuran have been demonstrated.[44,48]

1.2.5.1.1 Reactions with cyclopentadiene

Pyrrolizin-3-one **1** and 1- or 2-substituted pyrrolizin-3-ones act as 2π-electron components in [4+2] cycloaddition reactions with cyclopentadiene (Scheme 49). Generally, the adduct isomer ratio greatly favours the *endo* isomer over the *exo* isomer (Table 7).



1,16,18,20 **192-195**

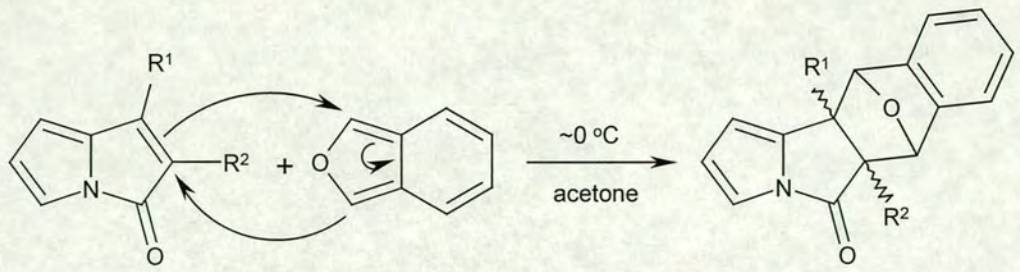
Scheme 49

Pyrrolizinone	Adduct	R^1	R^2	*endo*:*exo*	Yield (%)	Ref
1	**192**	H	H	95:5	84	**48**
16	**193**	CO_2Me	H	96:4	81	**44**
20	**194**	H	CO_2Me	48:52	89	**44**
18	**195**	H	CN	80:20	67	**44**

Table 7 – Yields and ratios of adduct formed with cyclyopentadiene

1.2.5.1.2 Reactions with isobenzofuran

The reaction of pyrrolizin-3-one **1** and 1- or 2-substituted pyrrolizin-3-ones with isobenzofuran (generated by FVP of 1,4-epoxy-1,2,3,4-tetrahydronaphthalene) is very similar to that with cyclopentadiene (section 3.4.1.1) but is performed at ~0 °C to prevent the polymerisation of isobenzofuran (Scheme 50). The *endo*/*exo* selectivity seems to be dependent on the pattern of substitution in the pyrrolizinones (Table 8).[44]



1,7,16-18,20 196-201

Scheme 50

Pyrrolizinone	Adduct	R^1	R^2	*endo*/*exo*	Yield (%)
1	**196**	H	H	90:10	87
7	**197**	Me	H	30:70	34
16	**198**	CO_2Me	H	96:4	81
17	**199**	H	Me	72:28	56
20	**200**	H	CO_2Me	35:65	99
18	**201**	H	CN	55:45	74

Table 8 – Yields and ratios of adduct formed with isobenzofuran

Reaction times vary considerably depending on the substituent present. Where the substituent is an electron-withdrawing group reactions are complete in the order of seconds whereas when the substituent is electron-donating reactions are much slower and some fail to reach completion due to the decomposition of isobenzofuran.[44]

1.2.5.2 1,3-Dipolar additions

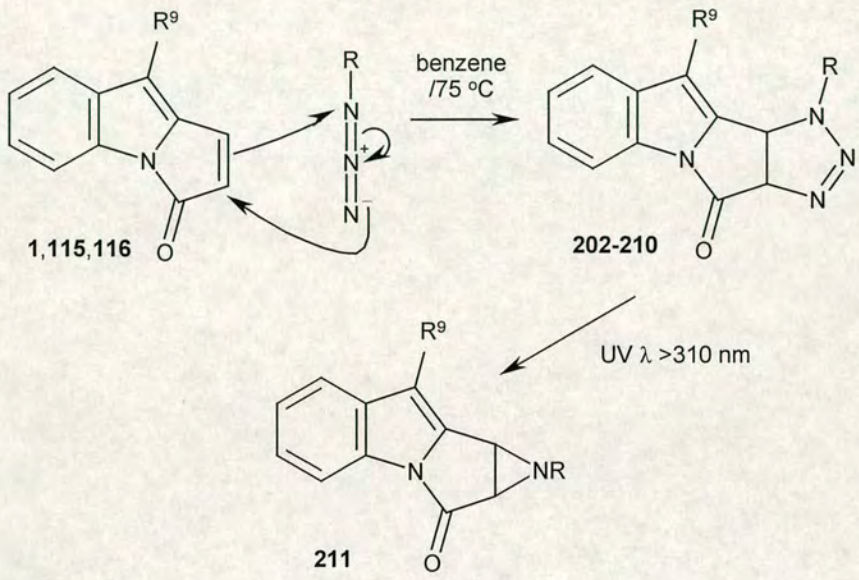
The enone double bond of the cyclopentenone ring in pyrrolizin-3-one **1** and in benzopyrrolizin-3-one **2** readily undergoes 1,3-dipolar cycloaddition reactions.[31,32,48]

1.2.5.2.1 Reactions with azides

A variety of azides has been used in cycloadditions with benzopyrrolizin-3-ones (Scheme 51, Table 9). The regiochemistry of the addition has not been proven but

has been assigned using precedents from Huisgen's work on dipolar additions of azides to dipolarophilic double bonds conjugated with carbonyls.[32,48]

Irradiation of the azide **202** with UV of wavelength ≥310 nm results in the photoelimination of molecular nitrogen to afford the aziridine **211** in high yield (Scheme 51).[32]



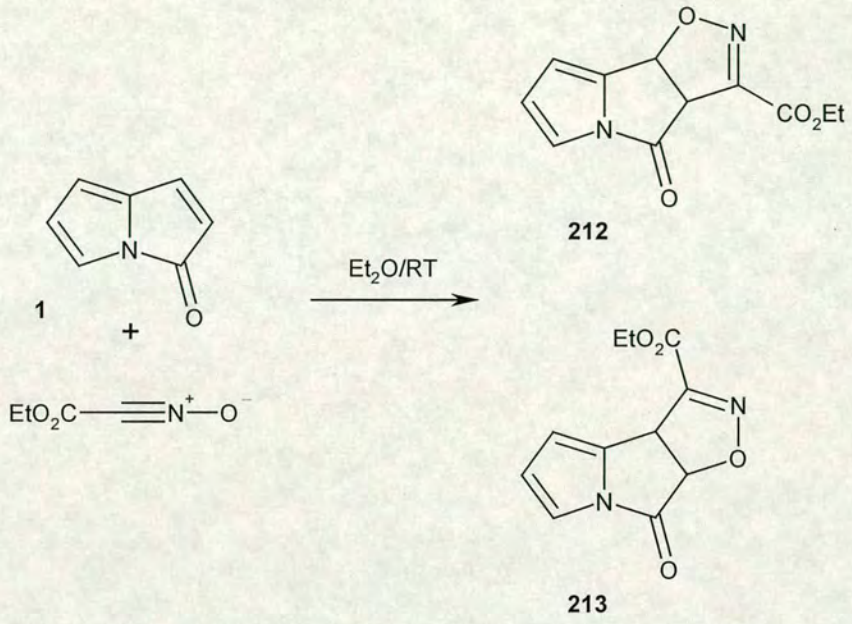
Scheme 51

Benzopyrrolizinone	Adduct	R^9	R	Yield (%)	Ref
1	**202**	H	Ph	54	**31**
1	**203**	H	CH_2Ph	54	**31**
1	**204**	H	Me	59	**31**
115	**205**	CH_2OMe	Ph	10	**32**
115	**206**	CH_2OMe	CH_2Ph	77	**32**
115	**207**	CH_2OMe	Me	55	**32**
115	**208**	CH_2OMe	CH_2OCH_2Ph	41	**32**
115	**209**	CH_2OMe	CH_2OMe	55	**32**
116	**210**	CH_2OCH_2Ph	CH_2Ph	47	**32**

Table 9 – Aziridines *via* 1,3-dipolar additions of azides

1.2.5.2.2 Reaction with ethoxycarbonylnitrile oxide

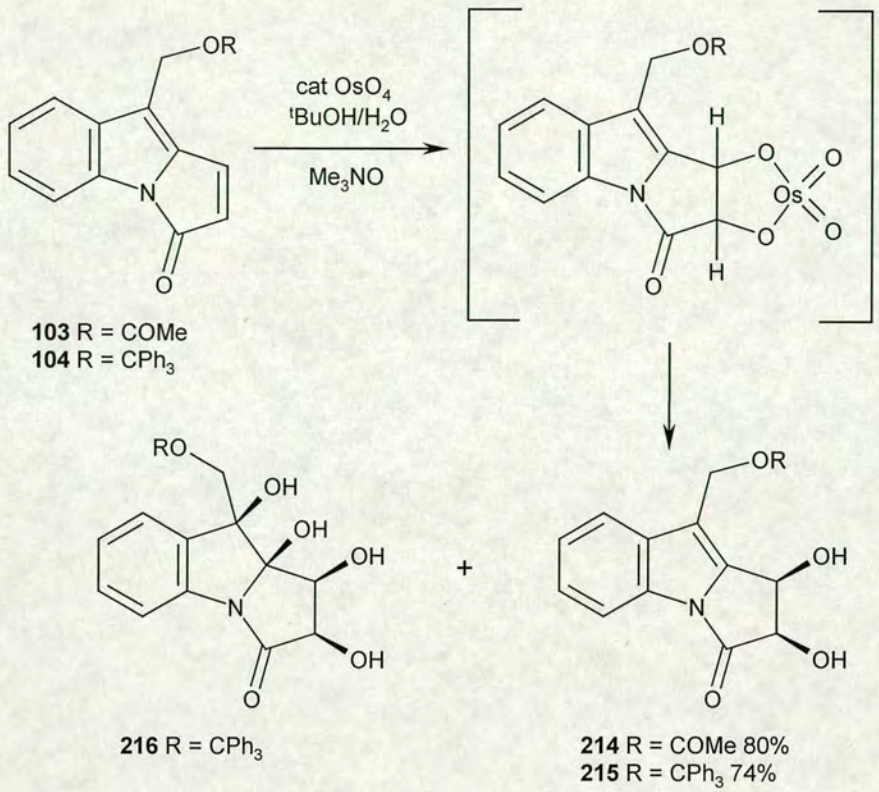
1,3-Dipolar cycloadditions of pyrrolizin-3-one **1** with ethoxycarbonylnitrile oxide, generated *in situ* from ethyl chloroximinoacetate, affords a 78:22 mixture of the isoxazolines **212** and **213** respectively in 62% yield overall (Scheme 52).[48]



Scheme 52

1.2.5.3 1,2-Diol formation with osmium tetroxide

The benzopyrrolizin-3-ones **103** and **104** can be readily oxidised to afford the 1,2-*cis* diols **214** and **215** respectively, and in the case of **104** even the tetraol **216**, by treatment with trimethylamine *N*-oxide and a catalytic amount of osmium tetroxide (Scheme 53).[26] Osmium tetroxide adds to alkenes to form 5-membered rings from which glycols can be obtained by treating with suitable salts to effect osmium-oxygen bond cleavage.



Scheme 53

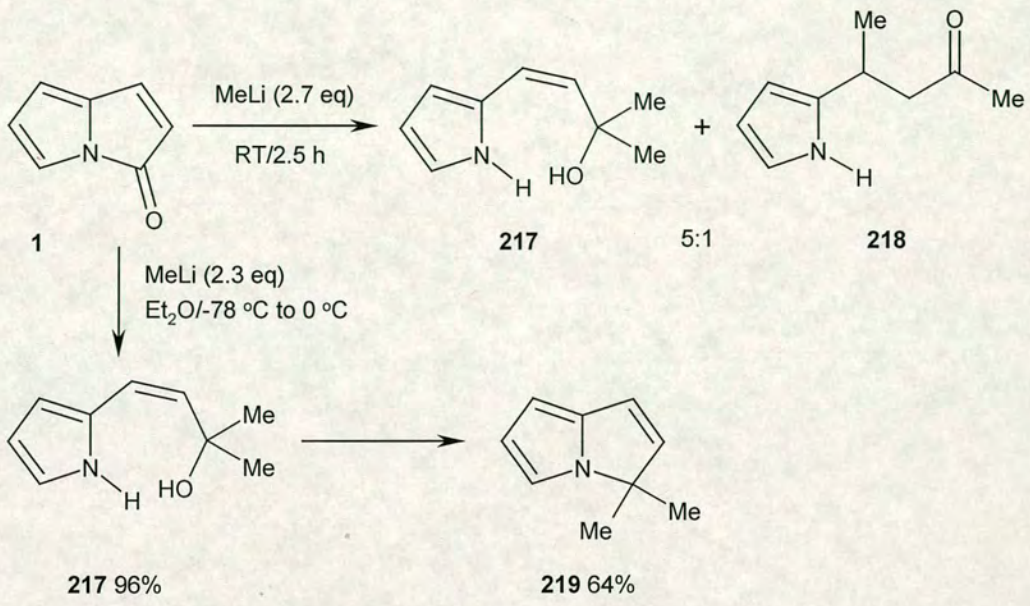
1.2.6 Reactions with organometallic species

Little investigation of pyrrolizinone reactivity towards organometallic species has been performed. No organometallic reactions with either the benzopyrrolizinone or isoindoloindolone systems have been reported.

1.2.6.1 Reactions pyrrolizin-3-one with organometallic species

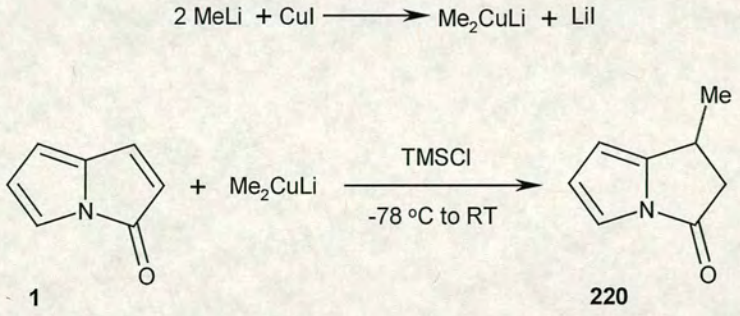
Addition of an ethereal solution of pyrrolizin-3-one **1** to an excess of methyl lithium at –78 °C and stirring at 0 °C for three hours generates the dimethyl allylic alcohol **217** as a result of nucleophilic methyl attack at the carbonyl centre.[50] The regioselectivity of this reaction appears to be temperature dependent and a ketone derivative **218**, that arises from a 'Michael' addition as well as nucleophilic methyl attack at the carbonyl centre, is also formed when the same reaction is performed at room temperature.[44] In a fashion analogous to that in section 1.2.3.4.1, the dimethyl

allylic alcohol **217** can undergo gas-phase pyrolysis to give 3,3-dimethylpyrrolizine **219** (Scheme 54).[50]



Scheme 54

Alternatively, the treatment of pyrrolizin-3-one **1** with dimethylcuprate in the presence of trimethylsilyl chloride at –78 °C and warming to 0 °C leads to the 'Michael' addition product 1-methyl-1,2-dihydropyrrolizin-3-one **220** as the only identifiable product in 15% yield (Scheme 55).[44]



Scheme 55

The ring-opened and 'Michael' addition products reflect the different selectivity of alkyl lithium and organocuprate species towards α,β-unsaturated carbonyl

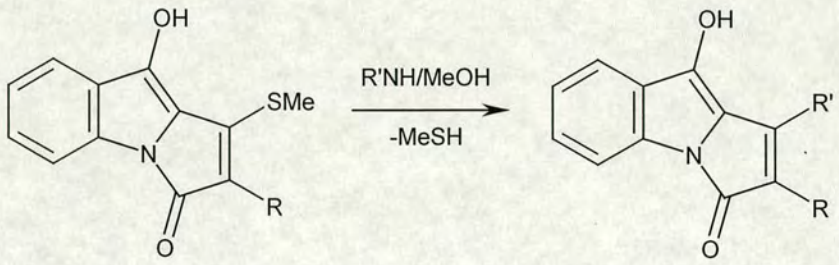
compounds. Grignard reagents, which have intermediate selectivity, do not react with pyrrolizin-3-one **1** at room temperature.

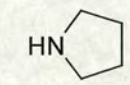
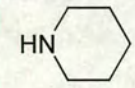
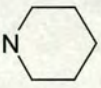
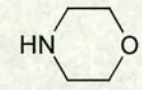
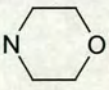
1.2.7 Substitution reactions

This section is concerned with reactions of benzopyrrolizin-3-one in which the skeleton remains unchanged.

1.2.7.1 Substitution reactions of substituted benzopyrrolizin-3-ones

Treatment of the tri-substituted benzopyrrolizinone **90** with pyrrolidine, piperidine or morpholine in methanol leads to substitution of the methylthio group giving the 1-amino products **221-223**. Similarly, the 1-carbomethoxy derivative **74** undergoes a substitution with benzylamine to afford **224** (Scheme 56).[53]

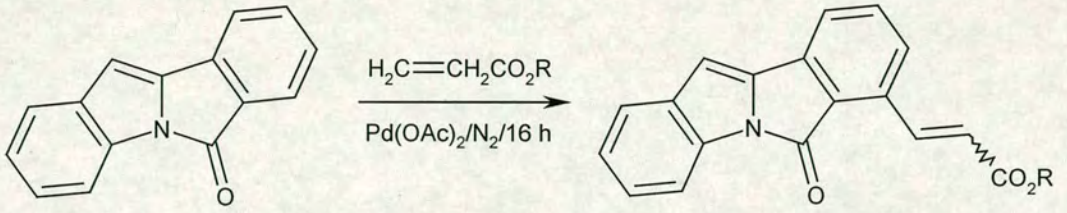


Benzopyrrolizinone	R	Amine	Product	R'N	Yield (%)
90	CN		**221**		70
90	CN		**222**		65
90	CN		**223**		65
74	CO_2Me	H_2NCH_2Ph	**224**	$HNCH_2Ph$	60

Scheme 56

1.2.7.2 Substitution reactions of isoindoloindol-6-one

During a study of the alkenylation of 1-acylindoles Itahara *et al* demonstrated that treatment of isoindoloindol-6-one **3** with palladium acetate and olefins such as methyl acrylate and ethyl acrylate gives the 11-substituted isoindoloindol-6-one derivatives **225** and **226** respectively (Scheme 57).[54]

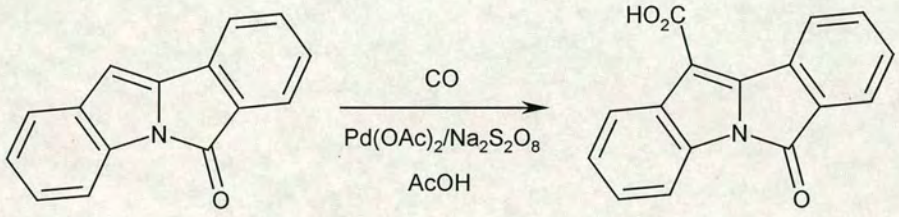


3

225 R = Me 48%
226 R = Et 50%

Scheme 57

Furthermore, Itahara found that bubbling carbon monoxide through a solution of isoindoloindol-6-one **3** in the presence of palladium acetate and sodium peroxydisulfate afforded the 11-carboxylic acid derivative **227** in 67% yield (Scheme 58).[55]



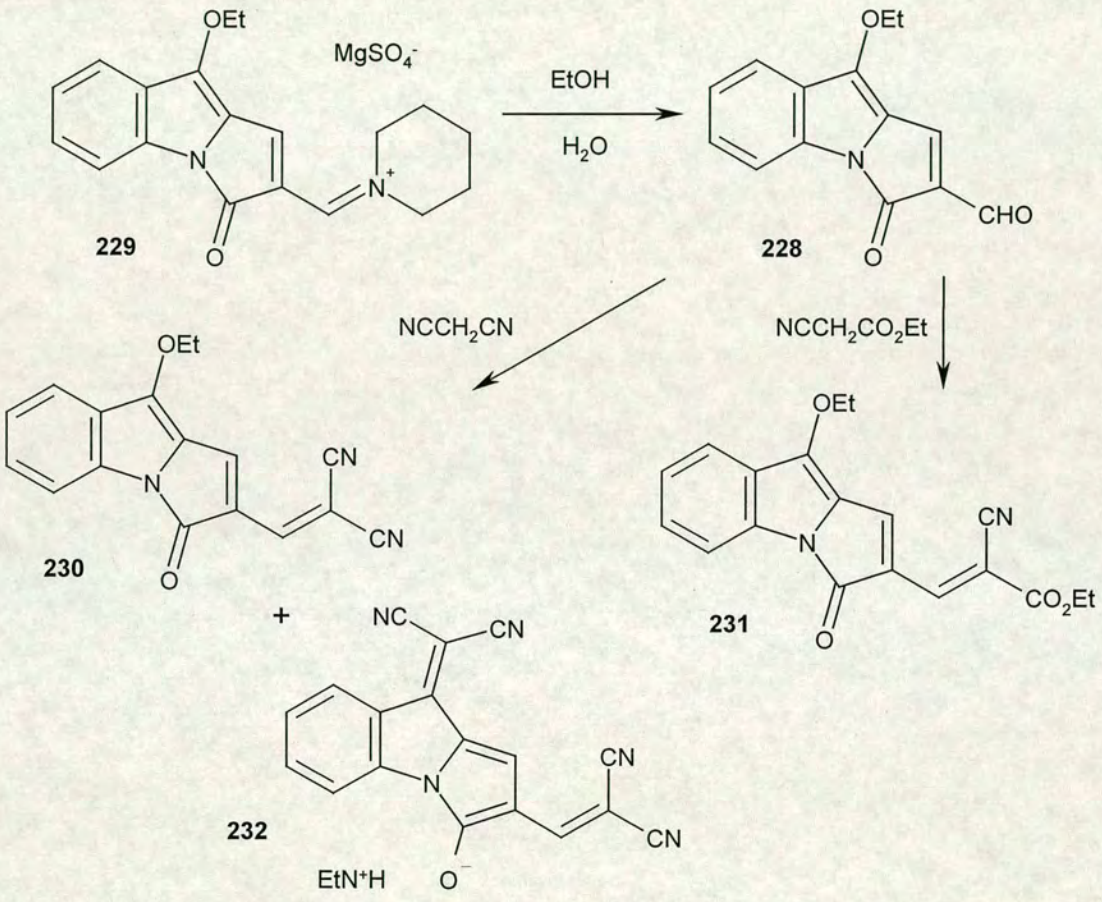
3 **227**

Scheme 58

The author suggests that the reactions are regioselective although no explanation is offered.

1.2.8 Reactions of substituents

9-Ethoxy-2-formylbenzopyrrolizinone **228**, obtained by treatment of the immonium salt **229** with ethanol/water, reacts readily with ethyl cyanoacetate or malononitrile in the presence of triethylamine to give the 2-vinyl derivatives **230** and **231** respectively. In the reaction with malononitrile a salt **232** is also obtained as a result of condensation of malononitrile at the 2- and 9-positions (Scheme 59).[49]



Scheme 59

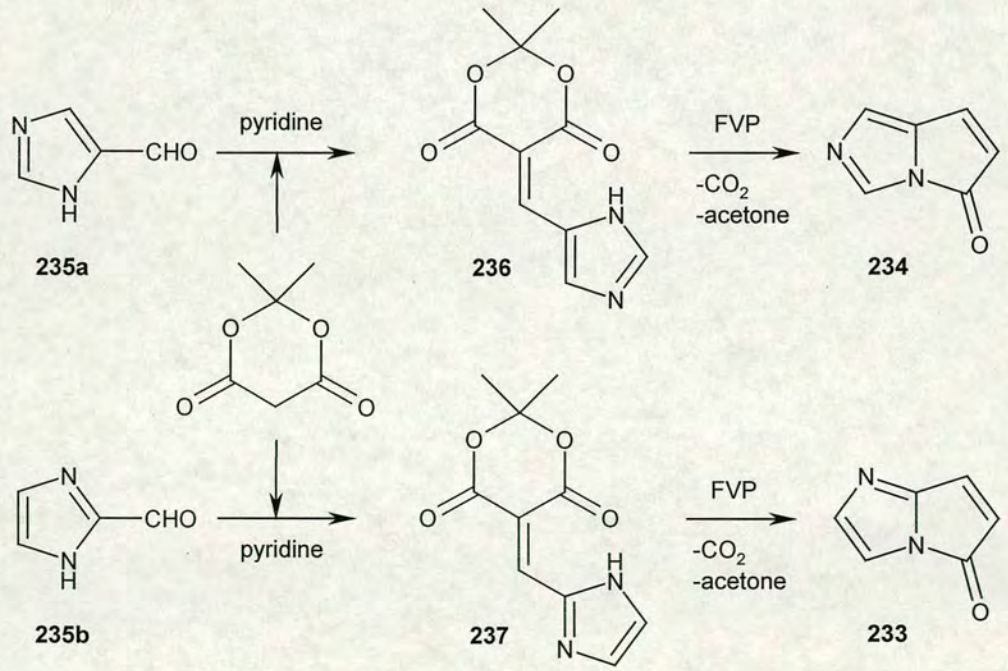
DISCUSSION

2.1 Formation of pyrrolo[1,2-*a*]imidazol-5-ones and pyrrolo[1,2-*c*]imidazol-5-ones

2.1.1 Introduction

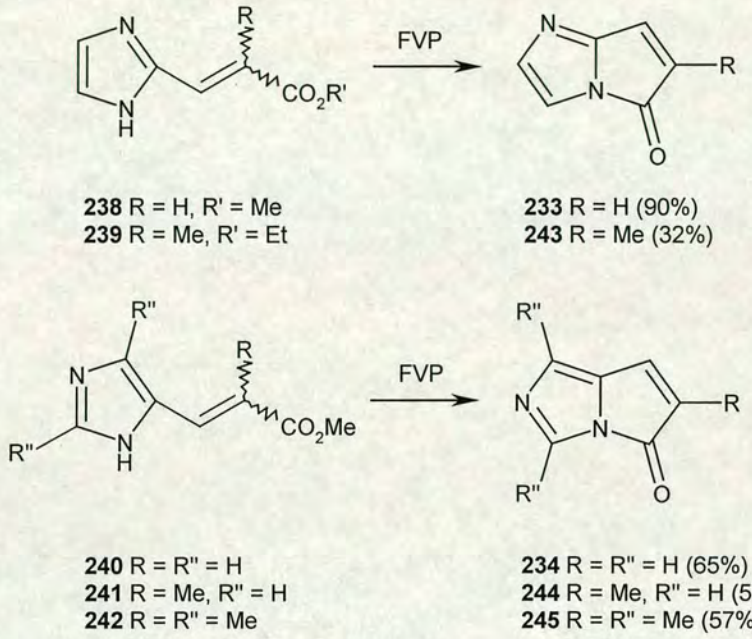
There are relatively few reports of pyrrolo[1,2-*a*]imidazol-5-one **233** and pyrrolo[1,2-*c*]imidazol-5-one **234** or their simple derivatives. Indeed, the major synthetic strategies involve flash vacuum pyrolysis (FVP) of Meldrum's acid derivatives or 3-azolylpropenoate precursors.[56,57] The unqualified term 'pyrroloimidazolone' refers solely to the 5-one isomer.

In the first pyrolytic route the precursors were prepared by condensation of an appropriate imidazolecarbaldehyde **235a** and **235b** with Meldrum's acid to give the derivatives **236** and **237**. Gas-phase pyrolysis of **236** afforded pyrrolo[1,2-*c*]imidazol-5-one **234** in 79% yield *via* an elimination/electrocyclisation mechanism (see section 1.1.1.1), but the extreme involatility of **237** meant that the yield of pyrrolo[1,2-*a*]imidazol-5-one **233** was substantially reduced (~6%) (Scheme 60).[56]



Scheme 60

The problem of low volatility and hence low yield was overcome by the use of 3-azolylpropenoates {formally 3-[imidazol-2(4)-yl]-acrylic acid esters} as precursors, obtained by reaction of imidazolecarbaldehydes with active methylene compounds. These precursors **238-242** were found to have good volatility and so proved to be more efficient in conversion to pyrroloimidazolones upon pyrolysis (Scheme 61).[57]



238 R = H, R' = Me
239 R = Me, R' = Et

233 R = H (90%)
243 R = Me (32%)

240 R = R" = H
241 R = Me, R" = H
242 R = R" = Me

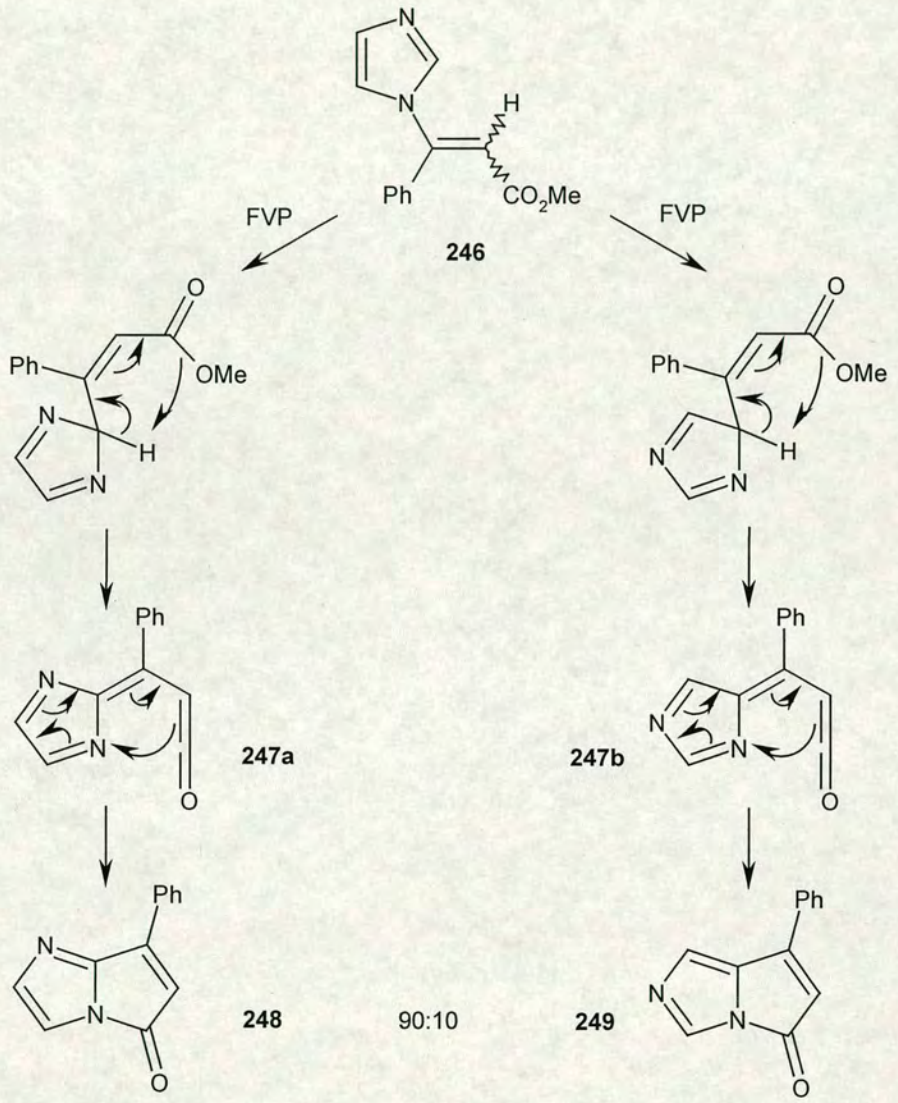
234 R = R" = H (65%)
244 R = Me, R" = H (59%)
245 R = R" = Me (57%)

Scheme 61

Recently a new 'cascade' process has been reported in which a more readily available imidazole *N*-propenoate precursor is pyrolysed. Upon pyrolysis of 3-(2*H*-imidazol-1-yl)-3-phenyl acrylic acid methyl ester **246** an irreversible nitrogen-to-carbon [1,5]-shift of the propenoate group occurs. The migration is followed by an elimination of methanol generating a ketene intermediate **247** that electrocyclises to afford 7-phenylpyrrolo[1,2-*a*]imidazol-5-one **248** and 7-phenylpyrrolo[1,2-*c*]imidazol-5-one **249** in a ~90:10 ratio respectively (Scheme 62).[11]

The conditions for full conversion of **246** to the pyrroloimidazolones **248** and **249** required a higher furnace temperature than previous elimination/electrocyclisation formations of pyrrolizinones. Temperature control studies using pyrrole 2-propenoates (of the type **5** R^1=R^2=H) showed (*E*)/(*Z*) isomerisation to be the rate controlling process in pyrrolizinone synthesis by FVP. Conversion to products of the

(*Z*)-isomer occurs at 650-700 °C whereas a similar percentage conversion of the (*E*)-isomer requires a furnace temperature of 850 °C. However, in the 'cascade' process it is not (*E*)/(*Z*) isomerisation that is the rate controlling step but the migration step indicated by the requirement for a higher furnace temperature (900 °C).



Scheme 62

The benefit of this route is that the pyrroloimidazolones are obtained in three steps from available starting materials in 79% overall yield whereas multi-step syntheses of imidazolecarbaldehydes are required in the previous methods. However, both isomers are formed, as opposed to the single isomer formation seen in the previous

methods, and this is a consequence of propenoate migration to either the 2- or 4-position of the imidazole. Such rearrangements are well known and migration to the 2-position is greatly favoured over migration to the 4-position.[58]

In order to further elucidate on the formation of pyrroloimidazol-5-ones by the 'cascade' process under FVP conditions a series of experiments was performed using *N*-propenoate precursors to demonstrate the generality of the synthetic methodology with the specific aims of:

i) establishing the effect of substituents at the 3-position of the propenoate on the degree of migration to the 2- and 4-positions and therefore the ratio of pyrroloimidazol-5-one isomers formed

ii) establishing the effect of a substituent at the 4-position of the imidazole ring of the precursor on the degree of migration to the 2- and 4-positions and therefore the ratio of pyrroloimidazol-5-one isomers formed

iii) attempting to direct the position of migration by blocking the 2- or 4- and 5-positions of the imidazole ring of the precursor to form single pyrroloimidazol-5-one isomers.

2.1.2 Preparation of precursors

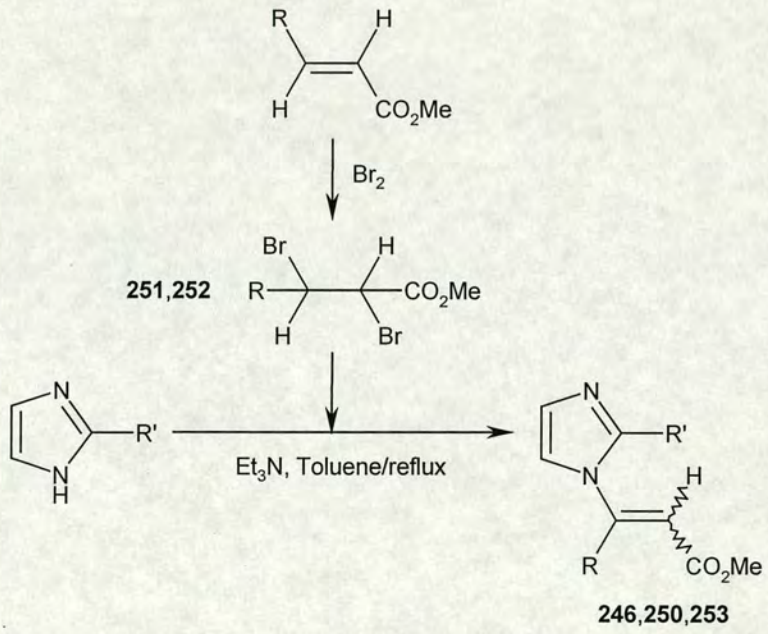
The precursors required for the study of the scope of pyrroloimidazol-5-one synthesis by FVP were prepared by one of two general routes: reaction of imidazoles with either 2,3-dibromopropanoic acid methyl ester derivatives or propynoic acid methyl ester.

2.1.2.1 Preparation of 3-(imidazol-1-yl)-3-substituted-acrylic acid methyl esters

The propenoate derivatives required as precursors in the preparation of isomer mixtures of pyrrolo[1,2-*a*]- and pyrrolo[1,2-*c*]imidazol-5-ones, compounds **246** and **250**, were prepared in two steps from available starting materials. The initial step involved the synthesis of the appropriate 2,3-dibromo compounds by addition of molar equivalents of bromine, added dropwise as solutions in DCM, to a cooled solution of either methyl *trans*-crotonate (to generate 2,3-dibromobutanoic acid

methyl ester **251**) or methyl *trans*-cinnimate (to give 2,3-dibromo-3-phenylpropionic acid methyl ester **252**). In each case the solution was allowed to stir until completely decolourised, indicating the completion of the reaction, after which removal of the solvent gave the compounds **251** and **252** in high yields (94% and 95% respectively) and in sufficiently pure form for further reaction.

The 2,3-dibromo esters **251** and **252** were reacted individually with a 1.5-fold excess of imidazole and 2-fold excess of triethylamine by heating under reflux in toluene for 18 h. Completion of the reactions was determined by T. L. C. analysis and dry flash chromatography proved to be the most efficient method of purification of the crude products **246** and **250**. The precursor **253** was also prepared from 2-methylimidazole by the same method (Scheme 63).



246,250,253

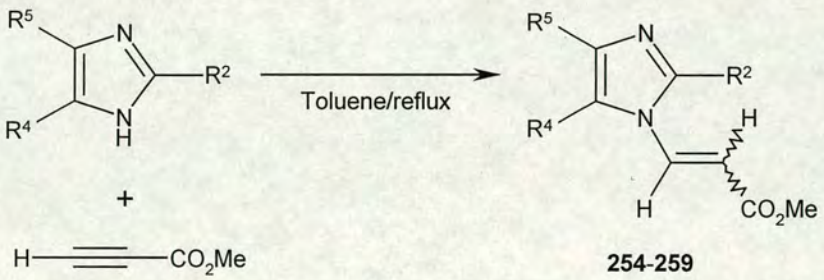
Product	R	R'	Yield (%)	Ratio *E/Z*
246	Ph	H	78	83:17
250	Me	H	47	80:20
253	Ph	Me	70	86:14

Scheme 63

Products, **250**, **246** and **253**, were obtained as geometric isomer mixtures. However, since (*E*)/(*Z*) isomerisation is an integral part of the elimination/cyclisation process under FVP conditions no attempt was made to separate the isomers. The (*E*) and (*Z*) configuration was assigned from the proton NMR spectra (see section 2.1.3.1) by evaluation of the clearly defined characteristic propenoate α-methine signal for each isomer between 5.7-6.5 ppm where the (*E*)-isomer signal is always at a higher chemical shift than the (*Z*)-isomer. Calculation of the isomer ratio was by measurement of the integrals of the α-methine signal for each isomer.

2.1.2.2 Preparation of 3-(imidazol-1-yl)-acrylic acid methyl esters

The majority of the precursors required for the study of the scope of pyrroloimidazol-5-one synthesis by the FVP rearrangement strategy were obtained by a general route involving the reaction of an appropriate imidazole with an equimolar quantity of propynoic acid methyl ester (Scheme 64, Table 10). Reactions were carried out in toluene under reflux and had a characteristic colour change from a clear solution to a deep yellow solution, with completion of the reaction determined by T. L. C. Purification was performed by one of several methods: recrystallisation, distillation or dry flash chromatography.



Scheme 64

Product	R^2	R^4	R^5	Yield (%)	Ratio *E/Z*
254	H	H	H	82	48:52
255	Me	H	H	55	100:0
256	Ph	H	H	61	66:34
257	H	Me	Me	79	67:33
258	H	Ph	Ph	59	88:12
259	H	CN	CN	6	90:10

Table 10 – Yields and *E/Z* ratios of 3-(imidazol-1-yl)-acrylic acid methyl esters

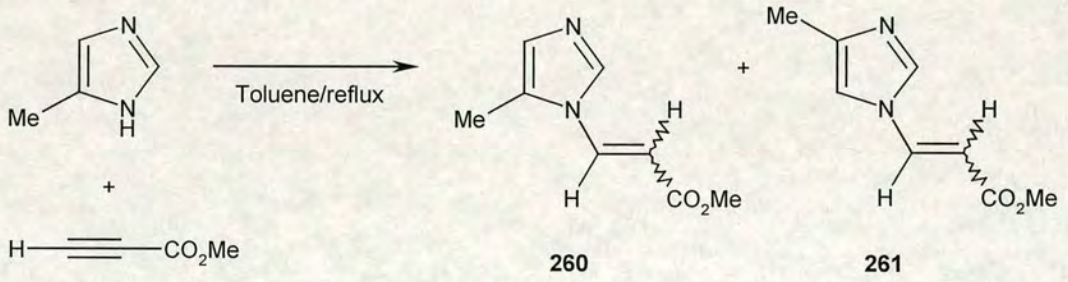
The 3-(imidazol-1-yl)-acrylic acid methyl esters **254-259** were generally obtained as geometric isomer mixtures that are easily distinguishable by ^{1}H NMR spectroscopy. In all case the coupling constants between the two alkene protons of the propenoate substituent are greater for the (*E*)-isomer (typically *J* 14.1-14.5 Hz) than the (*Z*)-isomer (typically *J* 10.3-10.6 Hz). 3-(2-Methylimidazol-1-yl)-acrylic acid methyl ester **255** was isolated exclusively as the (*E*)-configuration. Separation of the (*E*)- and (*Z*)-isomers of 3-(2*H*-imidazol-1-yl)-acrylic acid methyl ester **254** was achieved as a result of the crystallisation of the (*E*)-isomer from solution on cooling. Concentration of the filtrate under reduced pressure afforded crystallisation of pure (*Z*)-isomer.

Whilst the yields are reasonable for compounds **254-258**, the reaction of 4,5-dicyanoimidazole with propynoic acid methyl ester did not go to completion. The low yield of 3-(4,5-dicyanoimidazol-1-yl)-acrylic acid methyl ester **259** is therefore due to the deactivating effect of the strongly electron-withdrawing cyano groups on the imidazole nitrogen lone-pair hence reducing the potential for attack at the β–carbon of propynoic acid methyl ester. Insufficient material was obtained for pyrolysis.

To investigate the selectivity of propynoate addition a reaction using 4-methylimidazole was performed. For this to be useful for understanding further the

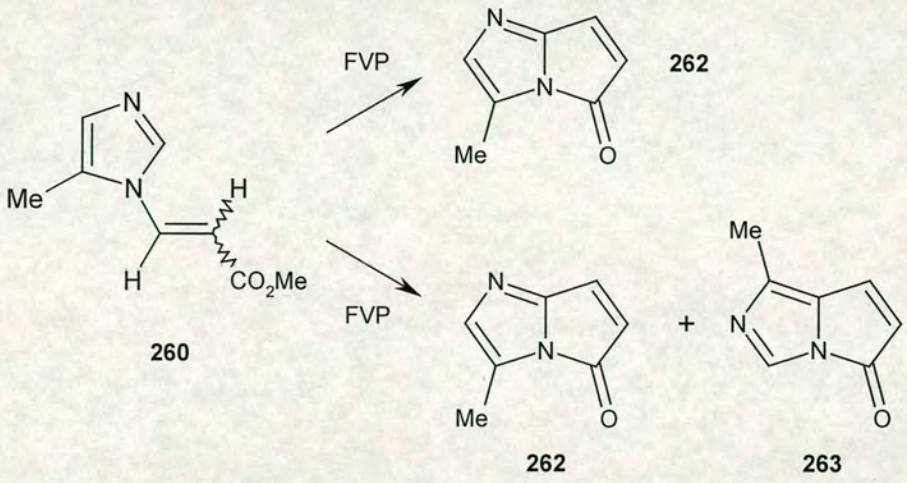
migration processes during FVP the propynoate would have to add to the more hindered site and any mixture of addition products would need to be separable.

4-Methylimidazole was reacted with propynoic acid methyl ester in toluene under reflux for 2 h. After removal of the solvent, distillation of the crude reaction mixture afforded a yellow oil. Inspection of the ^{1}H NMR spectrum showed four characteristic doublets pertaining to an α-methine proton of a propenoate carbon-carbon double bond in each case which indicated that the oil contained (*E*)- and (*Z*)-isomers of both 3-(4-methylimidazol-1-yl)-acrylic acid methyl ester **260** and 3-(5-methylimidazol-1-yl)-acrylic acid methyl ester **261** (Scheme 65). However, separation of the 4-methyl and 5-methyl products could not be achieved by distillation or by dry flash chromatography due to very similar R_f values in all eluents.



Scheme 65

Whereas nitrogen-to-carbon migrations are irreversible under FVP conditions carbon-to-carbon migrations are thought to be reversible.[58] The implications of these processes in the formation of pyrroloimidazol-5-ones under FVP conditions remains unknown but the precursor **260** may be expected to generate either 3-methylpyrrolo[1,2-*a*]imidazole-5-one **262** only or a mixture of 3-methylpyrrolo[1,2-*a*]imidazole-5-one **262** and 1-methylpyrrolo[1,2-*c*]imidazole-5-one **263** depending on the relative rates of the migration processes and the much greater tendency for migration from nitrogen to the imidazole 2-position (Scheme 66).



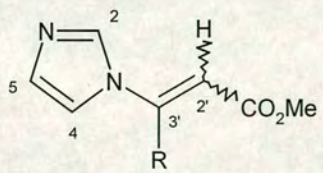
Scheme 66

2.1.3 Spectroscopic properties of *N*-imidazole propenoate precursors

The precursors were all characterised by ^{1}H NMR, ^{13}C NMR and mass spectroscopy and assignments of specific resonances by analogy with known imidazole *N*-propenoate and 2-propenoate derivatives. Although ^{13}C NMR spectra were recorded there are no specific carbon assignments since no HSQC experiments were performed. Where necessary elemental analysis and accurate mass have been recorded.

2.1.3.1 ^{1}H NMR spectra

The ^{1}H NMR spectra of all the precursors consist of two sets of signals which can generally be distinguished from one another. These sets of resonances are those associated with the imidazole (H-2, H-4 and H-5) and those associated with the propenoate (H-2' and H-3') moieties. Resonances are quoted according to the numbering system below.



The resonances associated with the imidazole ring vary substantially from those of imidazole[60] in some cases and their positions seem to be a result of the geometry of the propenoate functionality and imidazole substituents. The deshielding effect is largest in the (*Z*)-isomers and resonances for the H-2 protons may be shifted to significantly higher chemical shift, up to $\Delta\delta_H$ 1.1 ppm. A similar effect is also observed for the H-4, typically $\Delta\delta_H$ 0-0.4 ppm although it may be as much as $\Delta\delta_H$ 1.0 ppm for some (*Z*)-isomers.

For any precursor the chemical shift of the H-3' resonance (δ_H 6.53-8.08) is always greater than that of H-2' resonance (δ_H 5.44-6.83) as a consequence of conjugative electron withdrawal from the 3-position by the ester group and the deshielding effect of the imidazole ring. The ^{1}H-^{1}H coupling constants between H-2' and H-3', for both (*E*)- and (*Z*)-isomers, are comparable in value to those in similar systems such as crotonic acid ($^3J_{cis}$ 12.1 Hz and $^3J_{trans}$ 15.8 Hz) and cinnamic acid ($^3J_{cis}$ 12.3 Hz and $^3J_{trans}$ 16.0 Hz).[61,62] These differences in chemical shift and coupling constants have been used to assign the geometry in each instance.

Compound	Isomer	δ_H /ppm ($CDCl_3$)			
		H-2	H-4 and H-5	H-2' (Hz)	H-3' (Hz)
250	*E*	7.80	7.19 and 7.10	5.94	---
	Z	7.65	7.38 and 6.83	5.69	---
246	*E*	7.51	7.06 and 6.84	6.16	---
	Z	-[a]	7.01 and 6.98	6.06	---
253	*E*	---	6.98 and 6.73	6.47	---
	Z	---	6.86 and 6.77	5.95	---
254	*E*	7.74	7.18 and 7.03	6.01 (*J* 14.3)	7.86 (*J* 14.3)
	Z	8.02	7.79 and 7.02	5.44 (*J* 10.6)	6.85 (*J* 10.6)
255	*E*	---	7.15 and 6.97	5.93 (*J* 14.1)	7.84 (*J* 14.1)
256	*E*	---	7.40 and 7.18	6.09 (*J* 14.1)	8.02 (*J* 14.1)
	Z	---	7.99 and 7.20	5.61 (*J* 10.3)	6.93 (*J* 10.3)
257	*E*	7.70	---	6.00 (*J* 14.3)	7.68 (*J* 14.3)
	Z	8.53	---	5.67 (*J* 10.5)	6.79 (*J* 10.5)
258	*E*	8.06	---	6.07 (*J* 14.5)	7.54 (*J* 14.5)
	Z	8.73	---	5.54 (*J* 10.3)	6.53 (*J* 10.3)
259	*E*	8.76	---	6.83 (*J* 14.4)	8.08 (*J* 14.4)
	Z	-[a]	---	5.67 (*J* 12.1)	7.90 (*J* 12.1)

[a] – proton signal indistinguishable from other resonances with similar δ_H

Table 11 – Chemical shifts and coupling constants of 3-(imidazol-1-yl)-acrylic acid methyl esters

2.1.3.2 Mass spectra

The mass spectra of all the precursors contain strong molecular ion (M^+) peaks. The only exception is that of 4,5-dicyanoimidazole derivative that has a molecular ion peak of only 8%. The fragmentation patterns of all the spectra feature an initial loss of OMe (M^+ -31) followed by loss of CO (M^+ -31 -28) after which subsequent

fragmentations are complicated by competing pathways for the loss of substituents and imidazole fragmentation.

2.1.4 Flash vacuum pyrolysis

The gas-phase pyrolysis (performed as in section 3.2.9, Figure 14) of the *N*-imidazole propenoate precursors gave pyrroloimidazol-5-ones as either yellow liquids or solids. After removal of volatiles *in vacuo*, ^{1}H and ^{13}C NMR spectroscopy indicated that for small-scale pyrolyses (typically 40-100 mg) the pyrroloimidazolones were the sole products with little or no contaminant present. Large-scale pyrolyses (>150 mg) are subject to some degree of thermal decomposition at the furnace outlet causing the formation of insoluble polymeric side-products. However, this problem can be overcome by the use of a cold-finger trap (see section 3.2.9, Figure 15) that keeps the pyrroloimidazolone products cool for the duration of the pyrolysis.

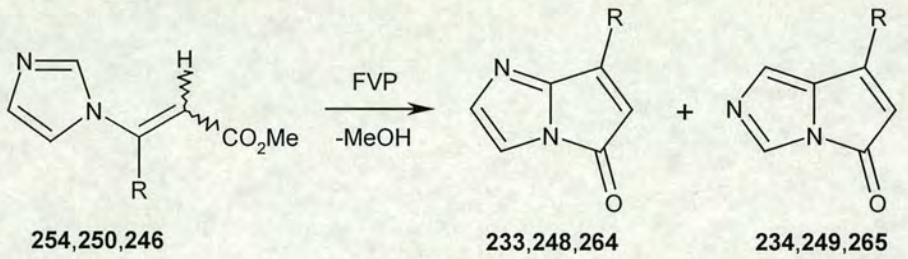
Purification of the pyrroloimidazolone products was not possible as these compounds are known to be highly unstable in air (probably irreversibly hydrolysed), in many solvents and on silica gel though they can be stored in sealed containers under nitrogen at –20 °C for some number of weeks.[56]

2.1.4.1 Pyrrolo[1,2-*a*]imidazol-5-one and pyrrolo[1,2-*c*]imidazol-5-one mixtures

Pyrolysis of 3-(imidazol-1-yl)-acrylic acid methyl ester **254** and the derivatives **246** and **250** all afforded mixtures of pyrrolo[1,2-*a*] and pyrrolo[1,2-*c*]imidazol-5-ones. Sublimation of the precursors was readily achieved with inlet temperatures of 110-140 °C and complete conversion of precursor to products was obtained with a furnace temperature of 850-900 °C over a period of 10-15 min. Upon completion of the pyrolysis the crude pyrolysates were dissolved into $CDCl_3$ for immediate NMR spectroscopic analysis.

Separate pyrolyses of the (*E*)- and (*Z*)-isomers of **254** both gave 73:27 isomer mixtures of pyrrolo[1,2-*a*]imidazol-5-one **233** and pyrrolo[1,2-*c*]imidazol-5-one **234** respectively by comparison of the ^{1}H NMR spectra of the crude pyrolysates with

literature chemical shifts. Similarly pyrolyses of isomer mixtures of **250** and **246** afforded pyrolysate mixtures of 7-methylpyrrolo[1,2-*a*]imidazol-5-one **264** and 7-methylpyrrolo[1,2-*c*]imidazol-5-one **265** and 7-phenylpyrrolo[1,2-*a*]imidazol-5-one **248** and 7-phenylpyrrolo[1,2-*c*]imidazol-5-one **249** respectively. In both cases the ratio of product formation was found to be 80:20 in favour of the [1,2-*a*] isomer (Scheme 67). A previous pyrolysis of **246** gave a 83:17 mixture of **248** and **249**.[45] The results show that there is no significant effect of propenoate 3-substitution on the ratio of migration to the 2- and 5-positions which for pyrolysis of imidazole *N*-propenoate precursors in which the imidazole ring is unsubstituted is 78±5:22±5. The formation of products derived from 2- and 5-position migration is unfavourable from a synthetic point of view. Although the products may be kept at –20 °C for some days they are unstable upon contact with air, many solvents and silica and therefore cannot be separated. Access to the individual isomer ring systems is still best achieved by pyrolysis of the appropriate imidazole 2- or 5-propenoate precursor (section 2.1.1).



254,250,246 **233,248,264** **234,249,265**

Precursor	R	Products	[1,2-*a*]/[1,2-*c*] ratio	Yield (%)
254 (*E*)	H	**233 234**	73:27	78
254 (*Z*)	H	**233 234**	73:27	80
246	Ph	**248 249**	80:20	76
250	Me	**264 265**	80:20	90

Scheme 67

2.1.4.2 Directed *N*-propenoate migrations

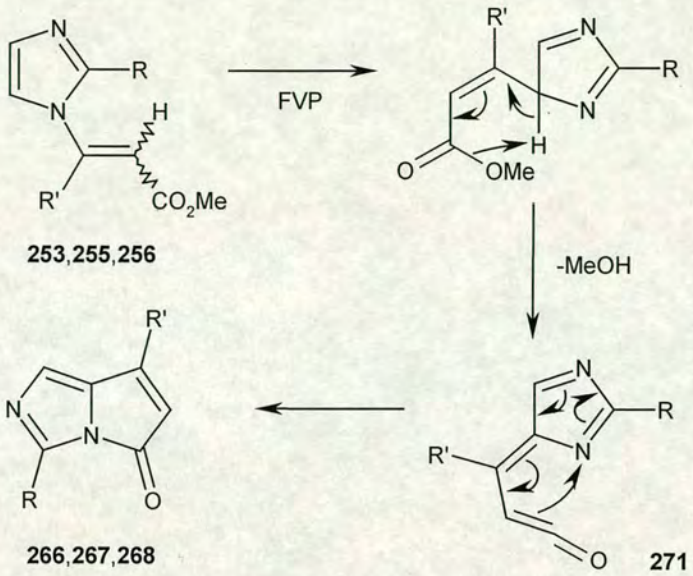
Blocking of either of the migration sites of the *N*-propenoate by the use of substituents at the 2-position or 4- and 5-positions of the imidazole ring of the precursor leads to single isomer pyrroloimidazolone products.

2.1.4.2.1 Pyrrolo[1,2-*c*]imidazol-5-ones

Pyrolysis of the precursors **253**, **255** and **256**, each with a substituent at the imidazole 2-position afforded the bright yellow analytically pure pyrrolo[1,2-*c*]imidazol-5-ones **266**, **267** and **268** in high yields (Scheme 68). Whereas pyrolysis of **255** required a furnace temperature of 875 °C, it was found that **256** could be effectively pyrolysed at 850 °C and **253** even lower at 825 °C. The variation in the required furnace temperature is most probably due to the effect of the substituents of the precursor on the energy needed for the nitrogen-to-carbon migration. Although the *E/Z* isomerisation of the (*E*)-propenoate is known to occur at temperatures between 825-875 °C no (*E*)-imidazole 2-propenoates, that would result from nitrogen-to-carbon migration but failure of the propenoate to isomerise to the (*Z*)-isomer required for cyclisation, were observed in any of the crude pyrolysates obtained from pyrolyses below the optimum temperature. All pyrolyses proceeded cleanly over a period of 7-10 min with little residue remaining at the inlet upon completion of the pyrolysis due to efficient sublimation of the *N*-propenoate precursors.

Since carbon-to-nitrogen migrations appear not to be possible, the substitution of the imidazole 2-position in the precursor must block the propenoate migration site entirely.[45,58] Indeed, no 2-*H* imidazole propenoate was observed in any of the crude pyrolysate and hence migration must be exclusively to the 5-position. It is likely that this is simply a steric effect. However, in appropriate cases, migration to a substituted site has been observed, *e.g.* in the pyrolysis of 2,5-dimethyl-1-(2-carbomethoxyphenyl)pyrrole **306** (section 2.3.2.1, Scheme 93). The various mechanistic questions opened up by this study might be appropriate for theoretical calculations [e.g. by Density Functional Theory (DFT) methods]. The single isomer products are obtained in high yield in just two steps from available starting materials

such that the route is the method of choice for the synthesis of appropriately substituted pyrrolo[1,2-*c*]imidazol-5-ones since it is also potentially general.



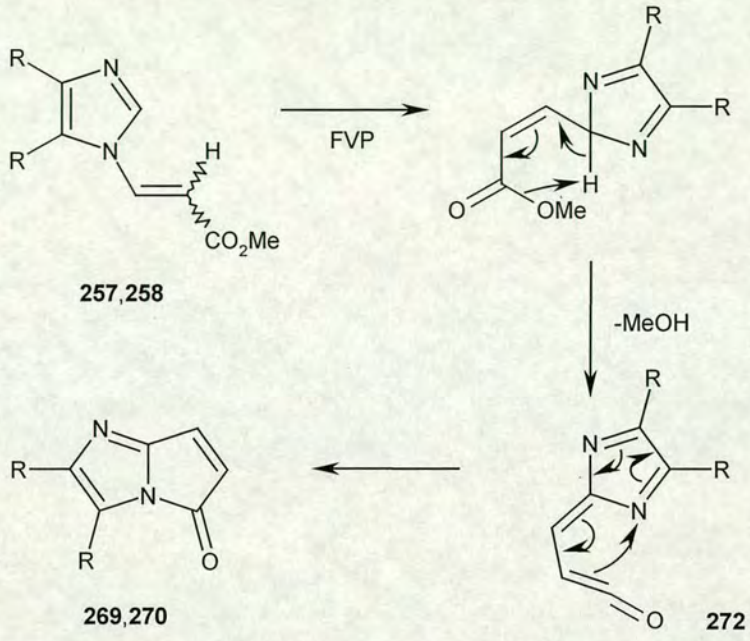
Precursor	R	R'	Product	Yield (%)
253	Me	Ph	**266**	91
255	Me	H	**267**	88
256	Ph	H	**268**	88

Scheme 68

2.1.4.2.2 Pyrrolo[1,2-*a*]imidazol-5-ones

In analogous fashion to the synthesis of pyrrolo[1,2-*c*]imidazol-5-ones (as above), the 4,5-disubstituted precursors **257** and **258** have given the pyrrolo[1,2-*a*]imidazol-5-ones **269** and **270** upon pyrolysis (Scheme 69). It was found that furnace temperatures of 850 °C and 825 °C respectively were required for optimum yields of products. The temperature variation presumably reflects the effect of the substituents on the energy required for propenoate migration, as previously stated, since no (*E*)-imidazole 2-propenoates were observed in the crude pyrolysates of pyrolyses performed below the optimum temperature. The pyrolyses were clean and high yielding with little or no residue at the inlet such that the method, like that used for

pyrrolo[1,2-*c*]imidazol-5-one synthesis (section 2.1.4.2.1), is the method of choice for obtaining the pyrrolo[1,2-*a*]imidazol-5-one ring system.



Precursor	R	Product	Yield (%)
257	Me	**269**	95
258	Ph	**270**	93

Scheme 69

2.1.5 Mechanism and scope of pyrroloimidazol-5-one synthesis by FVP of imidazole *N*-propenoate precursors

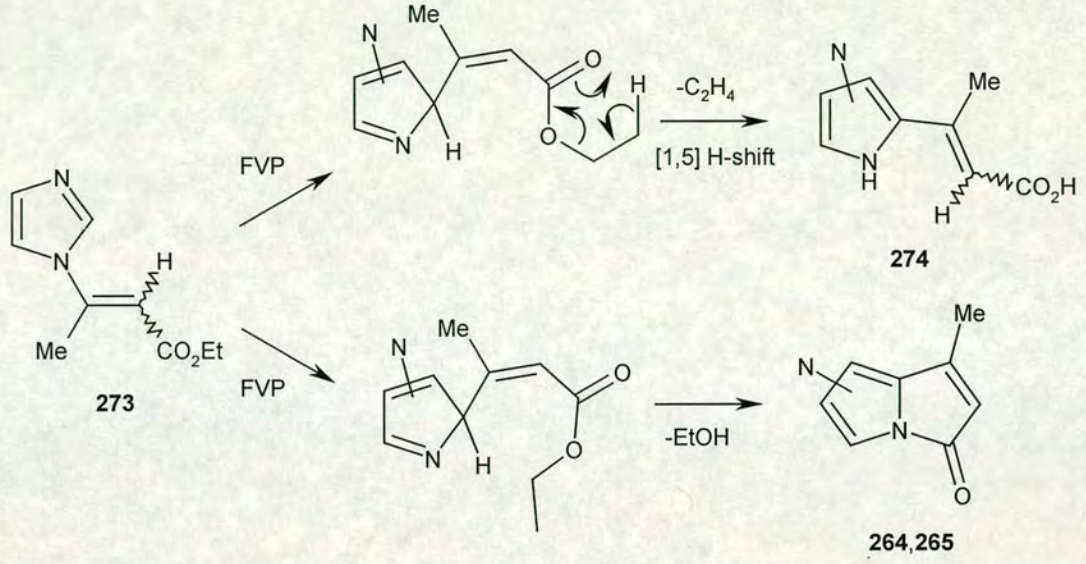
The mechanism of formation of pyrroloimidazolone products is as discussed in section 2.1.1 (Scheme 62) and in all cases involves initial migration of the *N*-propenoate group followed by generation of a ketene intermediate (of the type **247**) *via* the loss of methanol and electrocyclisation to the pyrroloimidazolone products.

From the pyrolyses of **246**, **250** and **254** it is clear that migration to the imidazole C-2 is strongly favoured giving ~80:20 ratio of pyrrolo[1,2-*a*] and pyrrolo[1,2-*c*]imidazol-5-one respectively in all cases within experimental error. A substituent at the 3-position of the propenoate has little effect on the degree of migration to either the imidazole C-2 or C-4 positions. However, it is apparent that the regioselectivity

of the propenoate migration is not as high as has been observed in other *N*-substituted imidazole migrations, for example the thermal migration of the phenyl group of 1-phenylimidazole gives 91% 2-phenylimidazole.[59]

The effect of the substituents at either the imidazole 2-position or 4- and 5-positions in the precursors is unambiguous. The irreversible nature of nitrogen-to-carbon migrations leads to the substituents blocking migration sites of the propenoate moiety affording single pyrroloimidazolone isomers. This route gives ready access to these compounds in overall yields of 48-75% in two steps from available starting materials and is advantageous because it negates the requirement for the multi-step synthesis of imidazole carbaldehydes as used in previous syntheses.[57] The pyrolysis step in all cases is efficient with yields ranging between 76-95% and is generally fast and clean without side-products.

A methyl ester affords the most efficient leaving group. Indeed it is necessary because whilst ethyl esters have been used in similar FVP syntheses of the pyrrolizin-3-ones **6** and **17** (section 1.1.1.1)[02,04], it has been shown that the use of analogous ethyl esters as precursors for pyrroloimidazol-5-one is not viable. Pyrolysis of 3-(imidazol-1-yl)-but-2-enoic acid ethyl ester **273** afforded a mixture of 1-methylpyrrolo[1,2-*a*] and [1,2-*c*]imidazol-5-ones **264** and **265** (60:40 respectively) and (*E*)/(*Z*) isomers of 3-(imidazol-2-yl)but-2-enoic acid **274** (50:50) in which the latter was by far the major component. The formation of the acids is a result of a 'retro-ene' reaction leading to the formation of propenoic acid derivatives of the precursors **274** followed by migration. These acids may also give lactam formation *via* the elimination of water and electrocyclisation. The small amount of pyrroloimidazolone products, that may result from migration and cyclisation of the ester **273** *via* loss of ethanol and cyclisation of the generated ketene intermediate or from **274**, do not reflect the true ratio of propenoate migration because any water generated as a side-product of cyclisation of **274** may ring-open **264** and **265** to give the (*Z*)-isomer of **274** due to the unstable nature of the products in the presence of water (Scheme 70).



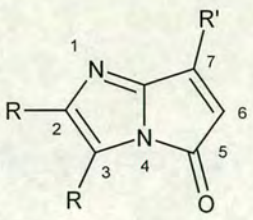
Scheme 70

2.1.6 Spectroscopic properties of pyrroloimidazol-5-ones

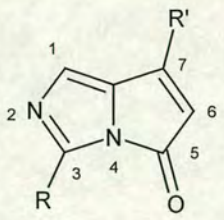
The pyrroloimidazol-5-one properties were characterised by NMR spectroscopy and mass spectroscopy. Due to the unstable nature of these compounds in air no elemental analyses were possible. However, where necessary accurate mass data were recorded. IR spectra were not recorded because of the potential instability of the pyrroloimidazolone products as mulls due to reaction with moisture. All of these compounds are brightly coloured and are usually yellow. This is a consequence of the conjugation of the ring system and is observed in similar ring systems such as pyrrolizinones.

2.1.6.1 ^{1}H NMR spectra

The proton NMR spectra of each of the pyrroloimidazol-5-ones prepared in this work have been assigned as fully as possible by comparison with literature data of the parent compound and substituted pyrroloimidazol-5-ones (Tables 12 and 13). Resonances for each pyrroloimidazol-5-one isomer are assigned according to the numbering sequence below.



[1,2-*a*]



[1,2-*c*]

Pyrrolo[1,2-*c*]imidazol-5-one	R	R'	H-1	H-3	H-6 (Hz)	H-7 (Hz)
234	H	H	6.74	7.69	5.79 (*J* 5.9)	7.26 (*J* 5.9)
265	H	Me	6.76	7.67	5.53	---
249	H	Ph	---[a]	7.80	6.01	---
267	Me	H	6.60	---	5.75 (*J* 5.7)	7.21 (*J* 5.7)
268	Ph	H	6.88	---	5.87 (*J* 5.9)	7.31 (*J* 5.9)
266	Me	Ph	7.02	---	6.06	---

[a] – proton signal indistinguishable from other resonances with similar δ_H

Table 12 – Chemical shifts and coupling constants of pyrrolo[1,2-*c*]imidazol-5-ones

Pyrrolo[1,2-*a*]imidazol-5-one	R	R'	H-2	H-3	H-6 (Hz)	H-7 (Hz)
233	H	H	6.90	6.97	5.96 (*J* 6.2)	7.17 (*J* 6.2)
264	H	Me	6.89	6.97	5.67	---
248	H	Ph	7.02	7.07	6.15	---
269	Me	H	---	---	5.88 (*J* 6.0)	7.08 (*J* 6.0)
270	Ph	H	---	---	6.02 (*J* 6.1)	---[a]

[a] – proton signal indistinguishable from other resonances with similar δ_H

Table 13 – Chemical shifts and coupling constants of pyrrolo[1,2-*a*]imidazol-5-ones

When R' is a methyl group, as in compounds **264** and **265**, the only significant effect is on H-6. Shielding by the mildly electron-donating methyl substituent causes the

resonance to move to lower chemical shift where $\Delta\delta_H$ = 0.26-0.29 ppm. The protons of the imidazole ring experience little or no effect as a result of the presence of the methyl group.

Similarly, when R' is a phenyl group, as in compounds **248** and **249**, there is also a significant effect on H-6. The electron-withdrawing nature of the phenyl substituent deshields H-6 by $\Delta\delta_H$ = 0.19-0.22 ppm. In **249** the H-1 resonance cannot be distinguished from the phenyl resonances but it is clear from the spectrum that it is not below δ_H = 7.0 ppm and so while the effect of the phenyl substituent on H-1 cannot be quantified it is significant. The protons of the imidazole ring also feel the effect with resonances shifted to high frequency by $\Delta\delta_H$ = ~0.1 ppm.

Methyl substituents on the imidazole ring, as in compounds **267** and **269**, only have a small effect on the H-6 and H-7 resonances moving them slightly to higher chemical shifts by $\Delta\delta_H$ = 0.04-0.09 ppm. In **267** the H-1 resonance does experience a significant shielding effect and its resonances are shifted to low frequency by $\Delta\delta_H$ = 0.14 ppm accordingly.

Phenyl substituents on the imidazole ring, as in compounds **268** and **270**, have the same effect as above but in the opposite direction. The resonances of H-6 and H-7 are shifted to high frequency by $\Delta\delta_H$ = 0.05-0.10 ppm. The H-1 resonance in **268** is shifted to higher chemical shift by $\Delta\delta_H$ = 0.14 ppm.

The resonances of H-1 and H-6 in **266** are both shifted to high frequency by $\Delta\delta_H$ = 0.28 ppm and $\Delta\delta_H$ = 0.27 ppm respectively. This result is similar to that of **249** and is presumably a result of the anisotropic effect of the phenyl substituent on the nearby H-1 and H-6 protons.

2.1.6.2 Mass spectra

The mass spectra of the pyrroloimidazol-5-ones have relatively little in common. The molecular ion (M^+) varies in intensity greatly (3-methylpyrrolo[1,2-*c*]imidazol-5-one **267** has M^+ 100% whereas 2,3-diphenylpyrrolo[1,2-*a*]imidazol-5-one **270** has M^+

15%) and the fragmentation patterns are complicated although each in each there is an initial loss of CO (M^+ -28).

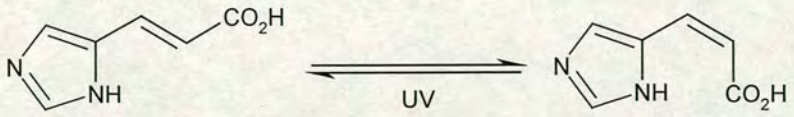
2.1.7 *cis*-Urocanic acids

The ability to access pyrrolo[1,2-*c*]imidazol-5-ones readily has the potential to give a new method for the synthesis of *cis*-urocanic acid derivatives by ring-opening of the amide bond by hydroxyl anions.

Urocanic acid [3-(imidazol-4-yl)-acrylic acid] is a naturally occurring component of the epidermis. The *trans*-isomer **275**, formed by deamination of histidine by the enzyme *histidase*, accumulates in the upper layers of the skin. Under UV radiation *trans*-urocanic acid is isomerised to give a ~50:50 mixture of *cis*- and *trans*-isomers that acts as a photoprotective agent, a natural sun-screen to protect DNA from UV damage.[63,64]

However, *cis*-urocanic acid **276** has also been shown to exhibit immunosuppressive behaviour and although the mode of action remains unclear it may have clinical applications in the prevention of the rejection of skin grafts and the treatment of diseases like psoriasis.[63,64]

At present the photoisomerisation of commercially available *trans*-urocanic acid is the only route to *cis*-urocanic acid but an equilibrium exists between the two isomers and is reached at ~70% *cis*-isomer after which chromatographic separation is required (Scheme 71).[65,66] A new FVP route has allowed access to *cis*-urocanic acids directly.

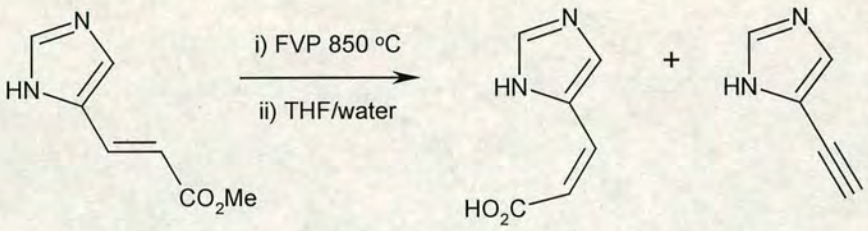


275 **276**

Scheme 71

2.1.7.1 Synthesis of *cis*-urocanic acid *via* FVP

An initial synthesis of **276** *via* an FVP route indicated that the process was viable but needed optimisation to afford **276** as the only product. The precursor **240** was pyrolysed at 850 °C and the products trapped on a cold-finger after which the pyrolysate was washed from the cold-finger and treated with neutral aqueous tetrahydrofuran then heated under reflux for three hours. After removal of the solvents the residues were separated chromatographically. It was found that during the pyrolysis of **240** a slight misjudgement of pyrolysis conditions (temperature control) had led to the formation of the 4-ethynylimidazole **277** that was isolated from the reaction products. This was presumed to be derived from the thermal degradation of **234** and such was the effect that the *cis*-urocanic acid **276** was obtained in only 46% yield after chromatographic separation (Scheme 72).[44]



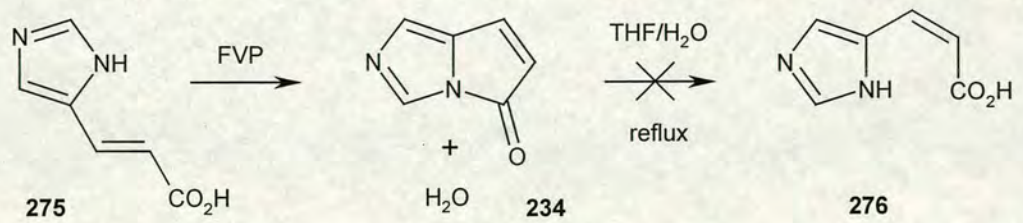
240 **276** **277**

Scheme 72

The precedent was clear and optimisation of the synthesis offered a two-step route to **276**. The pyrroloimidazolone **234** is very sensitive to air, solvents and silica and readily degrades under usual bench conditions such that handling the compound presents many problems. Usual techniques used for isolation/separation, removal of solvents and purification cannot be used for **234** or indeed any pyrroloimidazolone. A synthesis of **276** in which **234** is produced cleanly without the need for isolation/purification and can be ring-opened to **276** without the use of base (no need for chromatographic separation) is clearly advantageous. Such a synthesis has now been developed using a similar strategy involving an initial FVP route to **234** and ring-opening with neural aqueous tetrahydrofuran.

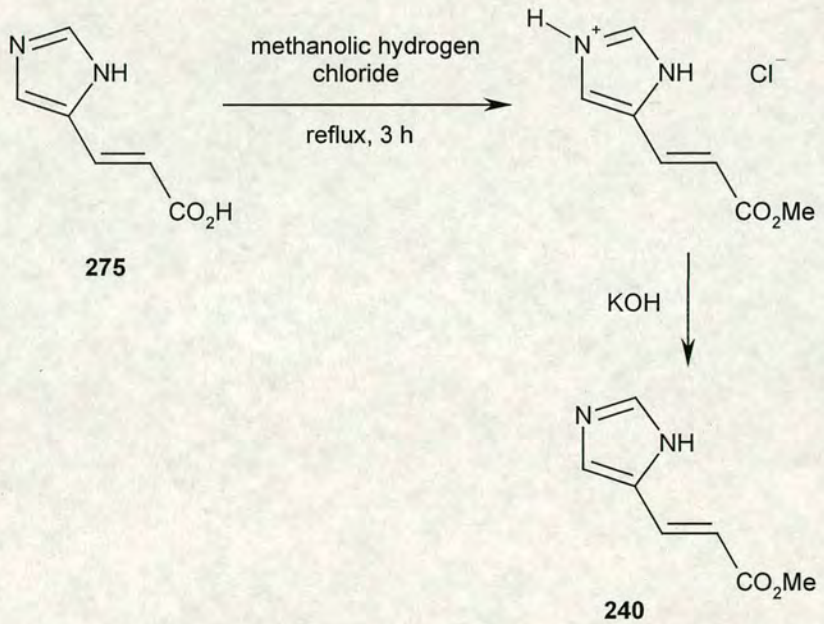
The first attempt to obtain *cis*-urocanic acid **276** by an FVP route involved using *trans*-urocanic acid **275** as the pyrolysis precursor. The pyrolysis of 100 mg of **275** using the standard FVP apparatus (section 3.2.9 Figure 14) with a furnace temperature of 850 °C to give optimum conversion to products afforded a solid yellow pyrolysate that was partially dissolved into a THF/water solution and heated under reflux for 4 h during which time no decolourisation was observed. This was a visual indication that the reaction was unsuccessful and after removal of the THF/water the solid residues were found to be mostly insoluble and were presumed to be polymeric material derived from **234**. The small amount of soluble residue was found to contain only trace quantities of *cis*-urocanic acid by ^{1}H NMR spectroscopy.

In an effort to prevent degradation of the pyrrolo[1,2-*c*]imidazol-5-one **234** at the trap during pyrolysis a cold-finger was used. The connection between the furnace tube and cold-finger was wrapped in foil to maximise condensation of the pyrolysate onto the cold-finger surface hence keeping it cold for the duration of the pyrolysis. Upon completion the products were rinsed, under nitrogen, from the cold-finger with a minimum volume of acetone and transferred to a round-bottomed flask. The acetone was removed at the oil pump to keep the pyrolysate cold and therefore prevent degradation. The solid product obtained was immediately treated with the THF/water solution as before but again the products were found to be largely insoluble (Scheme 73). The cause of failure of these reactions is unclear but the difficulty of handling **234** in any situation is certainly a problem. The extreme reactivity of **234** combined with the insoluble nature of the degradation material makes identifying the causes of degradation exceedingly difficult.



Scheme 73

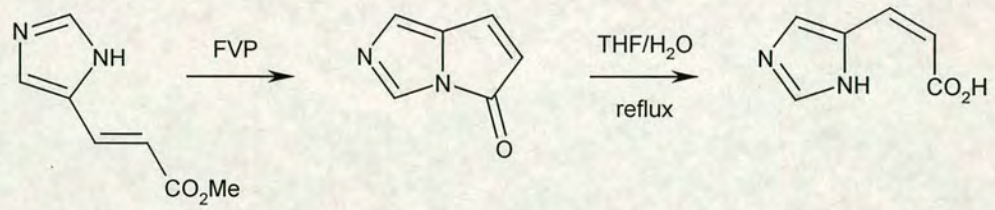
More efficient pyrolyses of precursors are achieved by the use of methyl esters instead of carboxylic acids. As a result it was decided to esterify *trans*-urocanic acid **275** to give a better precursor that would not generate water as a side-product but rather methanol which can be removed under vacuum upon completion of a pyrolysis reaction. In this way a far better yield of **234** could be obtained from which the *cis*-urocanic acid could be formed. *trans*-Urocanic acid **275** was dissolved into warm methanolic hydrogen chloride and the solution heated under reflux for 3 h. A precipitate formed on standing over 48 h and was collected by filtration to give *trans*-3-(imidazol-4-yl)-acrylic acid methyl ester **240** as a hydrogen chloride salt. The crystallised salt was combined with the concentrated filtrate and dissolved in water. Following treatment with potassium hydroxide (1 M) the solution continuously extracted with DCM over 24 h to afford **240** after drying and removal of the solvent (Scheme 74).



Scheme 74

A small-scale pyrolysis of **240** was performed with a furnace temperature of 850 °C using the cold-finger set-up as before. A yellow pyrolysate condensed on the cold surface and upon completion of the pyrolysis was rinsed from the trap with deuteriated chloroform. ^{1}H NMR spectroscopy showed the product to be the desired pyrrolo[1,2-*c*]imidazl-5-one **234**. Having found a suitable preparative method for the

synthesis of **234** a large-scale pyrolysis of 312 mg was performed under the same conditions. To avoid isolating **234** and risking degradation, the product was frozen directly into the THF/water solution on the cold-finger and allowed to warm to room temperature under nitrogen. The solution was then transferred to a round bottomed flask and heated under reflux for 3 h. Removal of the THF/water solution by rotary evaporator and drying at the oil pump afforded *cis*-urocanic acid as an off-white solid in 78% overall yield from **240** that was identified by comparison with literature ^{1}H NMR chemical shifts and coupling constants of the C-2 and C-3 propenoate protons for which *cis*-urocanic acid has *J* 12.9 Hz whereas *trans*-urocanic acid has *J* 15.6 Hz (Scheme 75).[67]

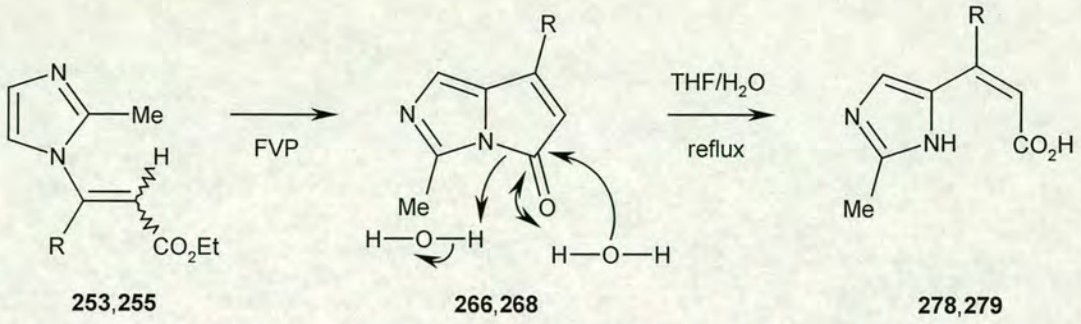


240 **234** **276**

Scheme 75

2.1.7.2 Synthesis of *cis*-urocanic acid derivatives *via* FVP

Pyrolysis, under conditions previously described, of the *N*-propenoates **255** and **253** led to the formation of the pyrrolo[1,2-*c*]imidazol-5-ones **266** and **268** respectively. Each of the pyrroloimidazolones were dissolved into a solution of tetrahydrofuran and water and heated under reflux during which time decolourisation occurred indicating the loss of the conjugation that gives pyrroloimidazolones such bright colour and hence completion of the reaction. Removal of the tetrahydrofuran and water *in vacuo* afforded the *cis*-urocanic acid derivatives **278** and **279** in good overall yield for the two steps (Scheme 76).



253,255 **266,268** **278,279**

Precursor	R	*cis*-Urocanic acid	Overall yield (%)
255	H	**278**	89
253	Ph	**279**	72

Scheme 76

The reaction involves addition of water across the amide bond and proceeds *via* attack of the 'hard' amide carbonyl carbon by a 'hard' water molecule causing cleavage of the amide bond to form the carboxylic acid product in which the geometry of the enone double bond has remained unchanged. The coupling constants of the C-2 and C-3 propenoic protons of **278** are 12.8 Hz indicating (*Z*)-isomer geometry of the product [coupling constants of the (*E*)-isomer are 15.6 Hz].[67] No measurement of coupling constants of **279** was possible due to the presence of a phenyl substituent at the propenoic C-3 position. A ^{1}H NMR spectrum showed two singlets at δ_H 7.14 ppm and δ_H 5.85 ppm pertaining to the imidazole C-5 proton and propenoic C-2 proton respectively and were assigned by comparison with the ^{1}H NMR spectra of **253** and **278**. A ^{1}H NMR NOESY experiment showed that the propenoic C-2 proton is close-in-space to the phenyl C-2 and C-6 protons but not the imidazole C-5 proton and therefore is exclusively the (*Z*)-isomer. An interaction between the propenoic C-2 proton and the imidazole C-5 proton and no interaction with the phenyl C-2 and C-6 protons would be expected if the ring-opened product contained any (*E*)-isomer (Figure 1). These interactions were not observed which indicates that there is no thermal or photolytic (since no attempt was made to perform the reaction in the dark) (*Z*)- to (*E*)-isomerisation. A similar ring-opening

reaction has been previously reported in which **234** was treated with methanol to give *cis*-3-(imidazol-4-yl)-acrylic acid methyl ester **240** as the only product.[44]

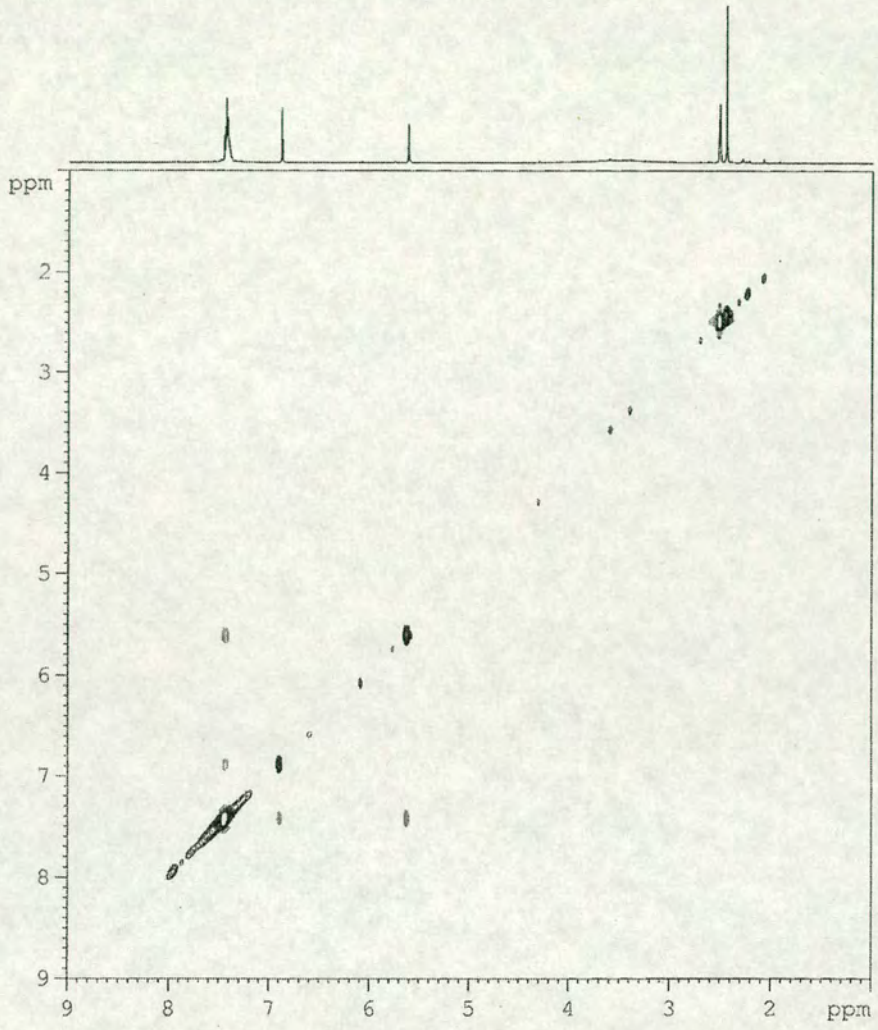


Figure 1 - ^{1}H NMR spectrum (360 MHz) and NOESY spectrum of **279**

The methodology employed for formation of **278** and **279** is not suitable for the synthesis of the parent *cis*-urocanic acid **276**. Synthesis by the conditions outlined above would require access to isolated pyrrolo[1,2-*c*]imidazol-5-one which cannot be achieved by the FVP method as described above since the precursor **254** gives a mixture of pyrrolo[1,2-*a*] and [1,2-*c*]imidazol-5-ones that cannot be separated.

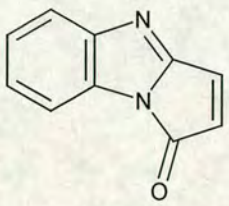
The FVP preparative method for *cis*-urocanic acids is general with the only limitation being that some substituents may not be suitable for FVP or the conditions

used during the ring-opening itself. The route is high yielding over the two steps, does not required the use of base and does not require chromatographic purification of the ring-opened products. It also offers ready access to the previously difficult to obtain parent *cis*-urocanic acid **276** as well and so is the method of choice for *cis*-urocanic acid synthesis.

2.2 Formation of azabenzo[1,2-*a*]pyrrolizinones

2.2.1 Introduction

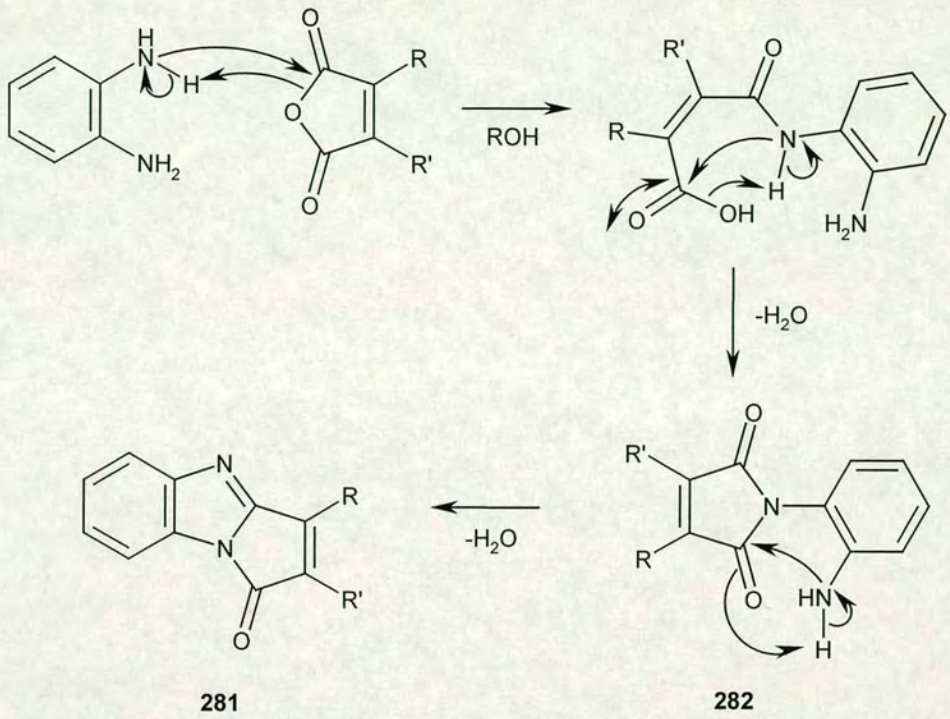
The use of imidazole *N*-propenoate precursors for pyrroloimidazol-5-one synthesis has proved to be very successful and in an extension of the methodology to *N*-propenoate precursors derived from benzimidazole has been used to give access to the azabenzo[1,2-*a*]pyrrolizinone system including the previously unreported parent compound, pyrrolo[1,2-*a*]benzimidazol-1-one **280**.



280

Very little on the synthesis, chemistry or properties of azabenzo[1,2-*a*]pyrrolizinones has been reported; known syntheses involve formation of the benzimidazole moiety from the reaction of 1,2-phenylenediamine with either maleic anhydrides or cyclobutene-1,2-diones.

The first synthesis of an azabenzopyrrolizinone, the annulated derivative **281**, was achieved by Bistrzycki in 1921 and involved the condensation of 1,2-phenylenediamine with phthalic anhydride in hot alcoholic solution. Initial amine attack at a carbonyl carbon leads to amide formation and subsequent loss of water gives the *N*-(2-amino-phenyl)phthalimide **282**. Condensation of the remaining amine group with a carbonyl functionality affords the derivative **281**. Similar syntheses have since been performed with a variety of maleic anhydrides (Scheme 77), however, hydroxyphenylmaleic anhydride did not react.



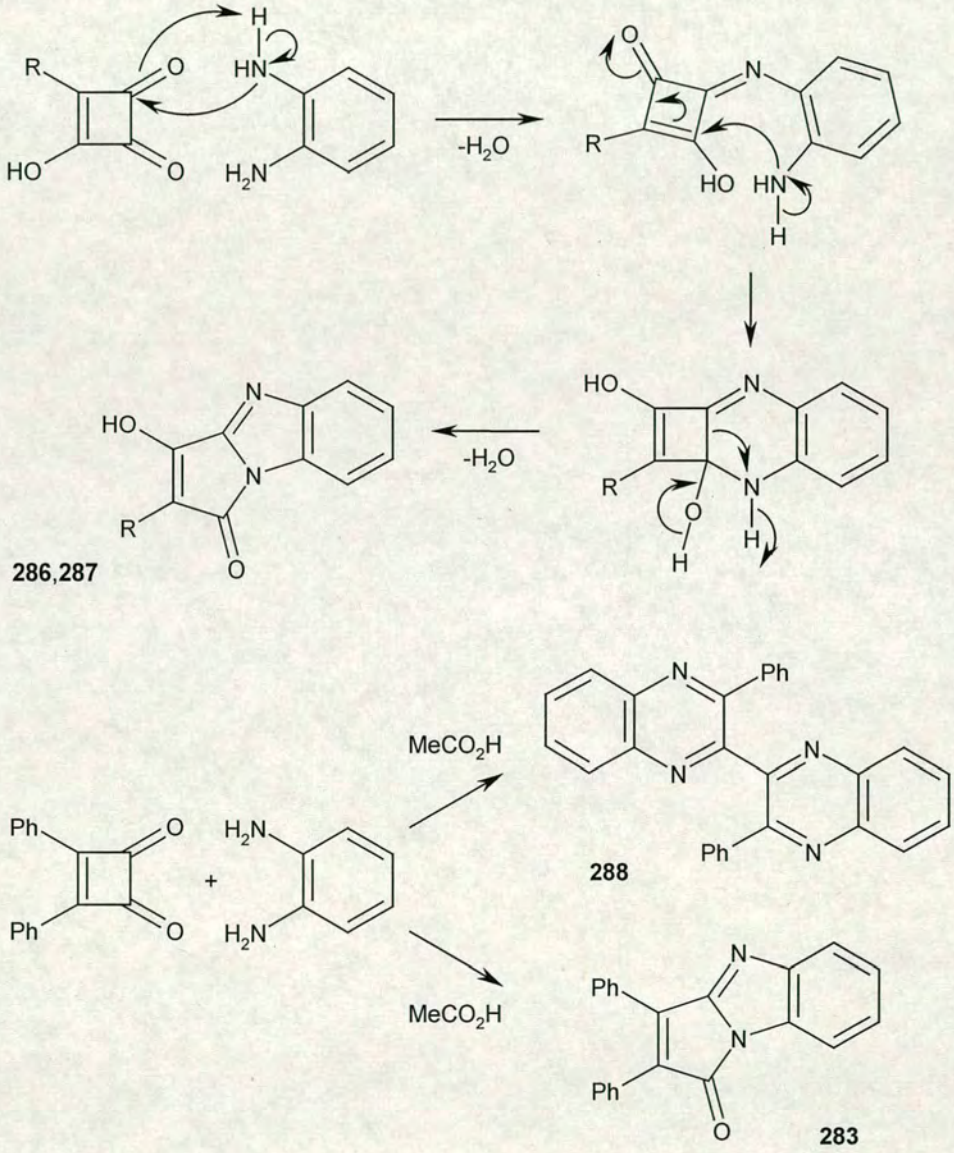
281 282

Product	R	R'	Yield (%)	Reference
281	(C_4H_4)		---	**68**
283	Ph	Ph	---	**69**
284	Me	Me	80-95	**70**
285	OMe	Ph	7	**71**

Scheme 77

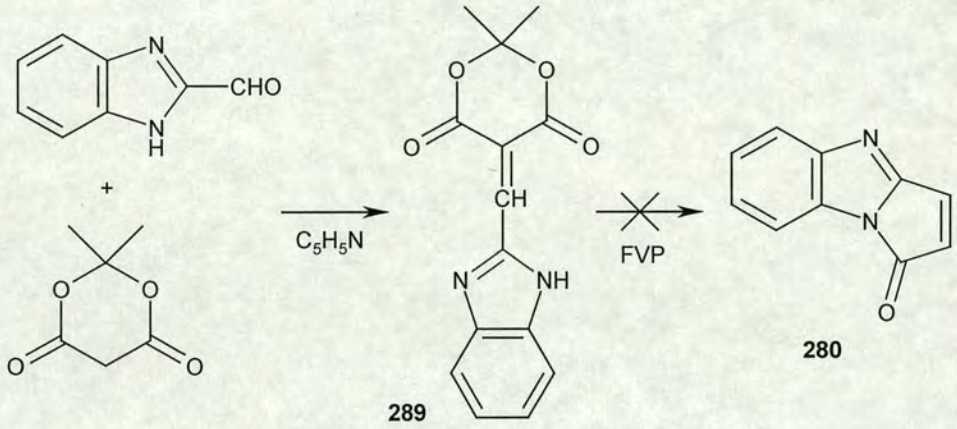
In the 1970s interest in cyclobutene-1,2-diones afforded other derivatives of **280** again *via* condensation with 1,2-phenylenediamine (Scheme 78). In the formation of **286** and **287** (where R = phenyl and 4-nitrophenyl respectively) the authors suggest that since hydroxyphenylmaleic anhydride does not react with 1,2-phenylenediamine,[71] the reaction must proceed *via* attack of an amine at the 2-carbonyl carbon followed by loss of water to generate the imine intermediate. A second amine attack at the hydroxyl carbon affords **286** and **287** in 75% and 70% yield repsectively.[72,73] In contrast **283** is formed from the reaction of 3,4-

diphenylcyclobutene-1,2-dione and 1,2-phenylenediamine in acetic acid in just 2% yield as a side product where the major product is 3,3'-diphenyl-2,2'-biquinoxaline **288** (Scheme 78). Such a difference in the reactivity of the cyclobutene-1,2-diones may indicate that the presence of the 3-hydroxyl functionality is necessary for azabenzopyrrolizinone formation.[74] Treatment of **286** with diazomethane gives **285** in quantitative yield.



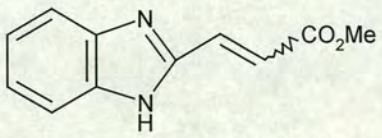
Scheme 78

Previous attempts to synthesis azabenzopyrrolizinone **280** by FVP methods have also failed. The problem is one of precursor synthesis where the analogous precursors to those used for pyrroloimidazol-5-ones described in section 2.1.1 (Scheme 1) are both unviable. The Meldrum's acid derivative **289** proved difficult to synthesise due to the insolubility of starting material (benzimidazole 2-carboxaldehyde) and problems in isolating the product such that **289** was obtained as a 1:1 complex with pyridine. Pyrolysis of **289** was not possible because of its involatility under FVP conditions (Scheme 79).[75]



Scheme 79

In 1974 Popov *et al* synthesised benzimidazole 2-propenoate **290** from a Wittig reaction of 2-formylbenzimidazole with methyl (triphenylphosphoranylidene) acetate. 2-Formylbenzimidazole usually polymerises but Popov *et al* claim that 2-formylbenzimidazole was depolymerised when heated under reflux in DMF and dimethyl sulfoxide such that a 70% yield of **290** was obtained.[76]



290

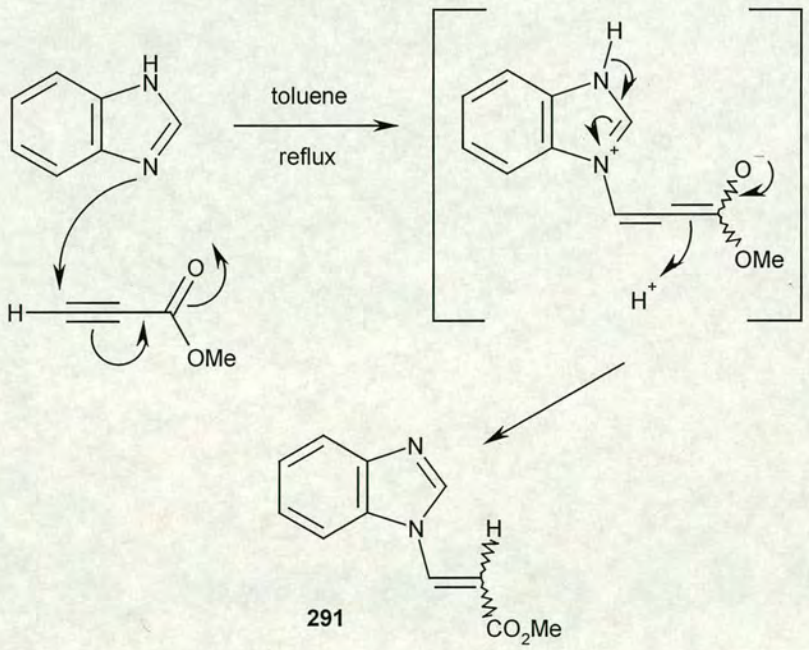
Bukowski also synthesised **290** but the synthesis involved four steps starting from malic acid and 1,2-phenylenediamine and the overall yield was low.[77] The

problematic synthesis of **290** is such that it has never been pyrolysed under FVP conditions.

The *N*-propenoate precursor rearrangement FVP route described in section 2.1 has been applied to the synthesis of azabenzo[1,2-*a*]pyrrolizinones since it offers ease of precursor synthesis.

2.2.1 Preparation of precursors

The precursor for azabenzo[1,2-*a*]pyrrolizinone **280** was readily prepared by the reaction of benzimidazole with propynoic acid methyl ester in toluene under reflux over 4 h to give a 44:56 (*E*)/(*Z*)-isomer mixture. The reaction occurs readily due to the presence of a non-delocalised nitrogen lone-pair that attacks at the β-carbon of propynoic acid methyl ester due to the resonance stability afforded by the ester moiety (Scheme 80). Recrystallisation in a minimum volume of toluene gave the pure precursor, 3-(benzimidazol-1-yl)-acrylic acid methyl ester **291**, in 95% yield.

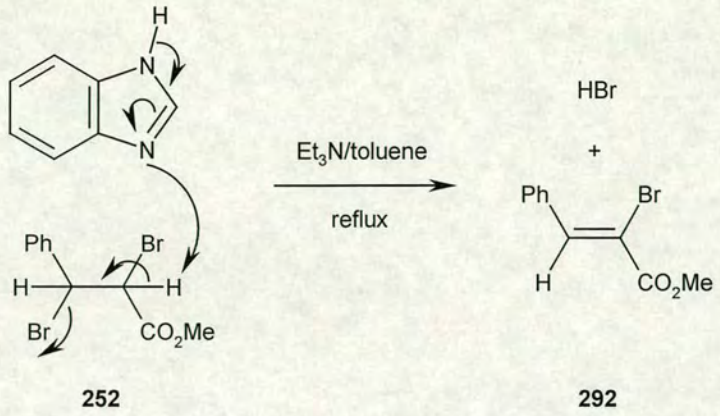


Scheme 80

Since the 2-position of the benzimidazole is required for propenoate migration under the rearrangement FVP route and the 4- and 5-positions are annulated no substituted benzimidazole precursors were synthesised. Substituents can be introduced on the propenoate and, unlike the pyrroloimidazol-5-one precursors **246** and **250**, may be expected to afford single azabenzopyrrolizin-1-one products upon FVP since the 4-position of migration is blocked in benzimidazole.

Analogous reactions to those used in the syntheses of **246** and **250** were performed using the 2,3-dibromopropanoic acid methyl ester derivatives **252** and **251** with benzimidazole rather than imidazole.

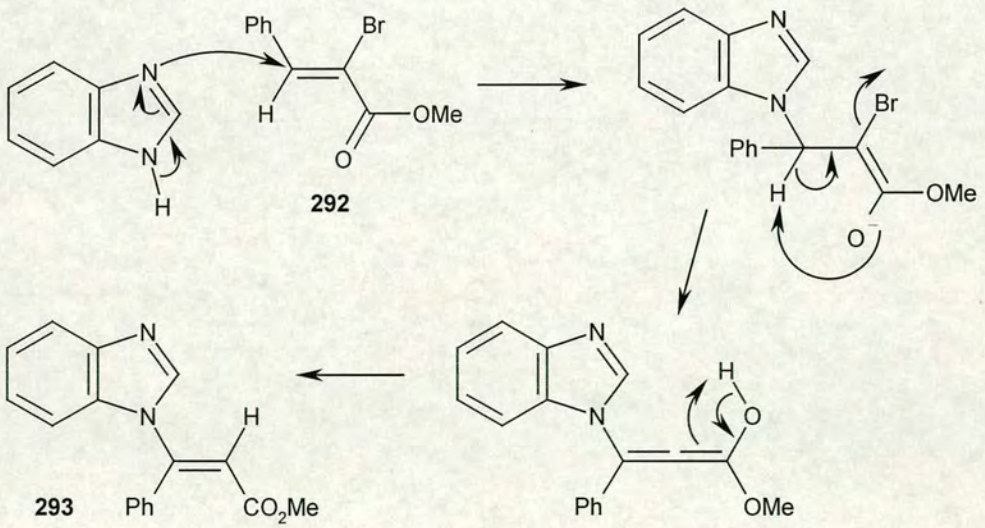
Benzimidazole and **252** were added together with an excess of triethylamine in toluene and heated under reflux for 5 h. After extraction into ether and removal of the solvent a high yield of material was obtained. The product was characterised by ^{1}H NMR spectroscopy and mass spectrometry. The ^{1}H NMR spectrum contained no benzimidazole type resonances but did have a proton singlet at δ_H 8.22 ppm, two sets of resonances in the aromatic region totalling five phenyl protons and a methyl singlet at the usual methyl ester position (δ_H 3.90 ppm). The proton singlet at δ_H 8.22 ppm is typical of that expected for a propenoate C-3 proton and the mass spectrum gave molecular ions at *m/z* 242 and 240 indicating the presence of bromine in the product so it was clear that the addition of benzimidazole had not occurred. The reaction product was identified as the α-bromopropenoate derivative **292** by comparison with literature spectra and was formed as a consequence of benzimidazole acting as a base, liberating hydrogen bromide, and not acting as a nucleophile (Scheme 81).[78]



252 292

Scheme 81

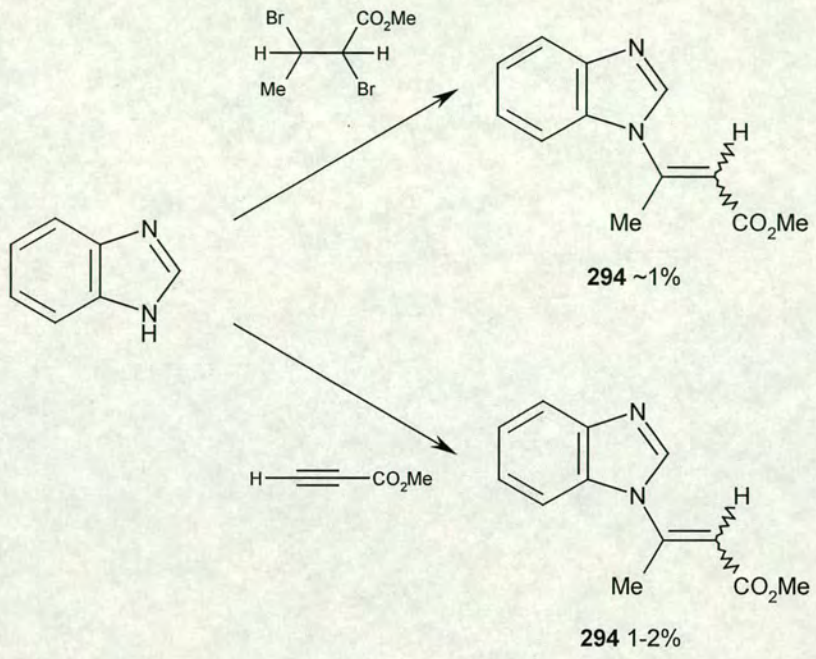
A second equivalent of benzimidazole was added together with **292** in toluene and the reaction heated under reflux for 24 h. Complete consumption of **292** was indicated by T. L. C. analysis after which the reaction products were extracted into DCM. Removal of the solvent and recrystallisation of the residues from toluene afforded the pure benzimidazole *N*-3-phenylpropenoate **293** in 21% yield (Scheme 82). The low yield may be due the combined effects of the steric bulk of benzimidazole and the electron withdrawing effect of the benzene ring reducing the nucleophilicity of the nitrogen lone-pair towards attack at the propenoate β-carbon.



Scheme 82

The precursor was isolated as exclusively the (*E*)-isomer as indicated by comparison of the chemical shift of the propenoate C-2' proton (δ_H 6.43 ppm) with that of the imidazole analogue **246** [where (*E*)-H-2' δ_H 6.16 ppm] and is typical for (*E*)-isomers; those of (*Z*)-isomers are always of lower frequency (see section 2.1.3.1). Whereas **246** was obtained as both (*E*)- and (*Z*)-isomers, the steric bulk of benzimidazole may be the reason for the formation of the (*E*)-isomer only in this case.

The reaction of benzimidazole with **251** under the same conditions as used for the reaction with **252** was unsuccessful. Heating under reflux for 30 h and extraction of the organic residues into ether afforded very little material. A proton NMR spectrum showed that no α-bromopropenoate derivative was present as observed in the initial reaction of benzimidazole with **252**. Kugelrohr distillation gave impure benzimidazole *N*-3-methylpropenoate **294** in ~1% yield. The recovery of only small quantities of organic material suggests that the reagents may have formed salts with triethylamine and therefore were lost during the extraction into ether (Scheme 83).
Synthesis of **294** was also attempted using methyl 2-butynoate. Benzimidazole and a molar equivalent of methyl 2-butynoate were added together in toluene and heated under reflux for 18 h after which a proton NMR spectrum of a sample of the crude reaction mixture showed some formation of **294**. Addition of a second equivalent of methyl 2-butynoate and heating another for 12 h afforded no further reaction. Removal of excess methyl 2-butynoate and toluene followed by extraction of the organic residues into DCM gave only 1-2% of **294** (Scheme 83).



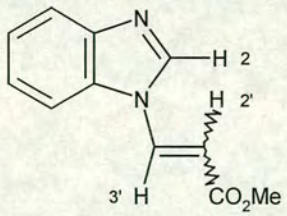
Scheme 83

2.2.2 Spectroscopic properties of benzimidazole *N*-propenoates

Characterisation of **291** and **293** was by ^{1}H NMR, ^{13}C NMR and mass spectroscopy. The assignment of specific resonances is by direct comparison with the spectra of the imidazole *N*-propenoates (section 2.1.2). No HSQC experiments were performed such that no specific carbon resonances are defined.

2.2.2.1 ^{1}H NMR spectra

The phenyl resonances in the ^{1}H NMR spectra all occur in the usual aromatic region (between δ_H 7.9-7.1 ppm) and are not specifically assigned. However, the benzimidazole C-2 proton and the propenoate C-2' and C-3' protons have been assigned (Table 14).



Product	Isomer	δ_H /ppm ($CDCl_3$)		
		H-2	H-2' (Hz)	H-3' (Hz)
291	*E*	8.06	6.14 (*J* 14.5)	7.96 (*J* 14.5)
	Z	9.09	5.52 (*J* 10.4)	6.94 (*J* 10.4)
293	*E*	8.00	6.43	---

Table 14 – Chemical shifts and coupling constants of 3-(benzimidazol-1-yl)-acrylic acid methyl ester

The H-2 resonance of (*Z*)-**291** is shifted to significantly higher frequency ($\Delta\delta_H$ 1.07 ppm) compared with that of (*Z*)-**254** and is presumably a result of the close proximity of the ester moiety combined with the conjugative electron withdrawing effect of the benzimidazole benzene ring. A similar but smaller shift ($\Delta\delta_H$ 0.32 ppm) is present in (*E*)-**291** compared with (*E*)-**254** where the ester moiety is not in such close proximity to the H-2 proton and so has less effect.

The chemical shift values of the H-2' and H-3' resonances of both (*E*)- and (*Z*)-isomers are very similar to those of the analogous imidazole **254** with H-3' at higher chemical shift than H-2'. The coupling constants of both the (*E*)- and (*Z*)-isomers also show negligible difference in their values from those of **254** and have been used to assign the geometry of the propenoate.

In **293** both the H-2 and H-2' resonances are shifted to higher frequency by $\Delta\delta_H$ 0.27-0.49 ppm relative to the imidazole analogue **246** as a consequence of the benzene ring of benzimidazole increasing the deshielding effect.

2.2.2.2 Mass spectra

The electron impact spectra are clear and both **291** and **293** show strong molecular ions (M^+). The fragmentation patterns show losses of Me (M^+ -15), OMe (M^+ -31) and CO_2Me (M^+ -59) after which the propenoate alkene moiety (with any substituent)

is lost giving a peak at *m/z* 118 that pertains to benzimidazole which then itself undergoes further fragmentation with the loss of HCN and N to give peaks at *m/z* 91 and 76 respectively.

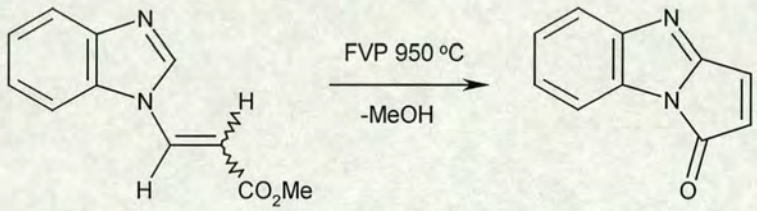
2.2.3 Flash vacuum pyrolysis

Gas phase pyrolysis of the precursors **291** and **293** gave pyrrolo[1,2-*a*]benzimidazol-1-ones **280** and **295** respectively as yellow solids. Small-scale pyrolyses (25-50 mg) were performed using apparatus as shown in section 3.2.9 (Figure 14). Pyrolyses at 850 °C, 900 °C and 950 °C indicated that optimum conversion of precursors to products was at 950 °C. The low volatility of the precursor was also apparent and complete volatilisation of the starting material required heating the inlet to temperatures of around 200 °C.

After removal of volatiles *in vacuo* the pyrolysates were dissolved into deuteriated chloroform for immediate NMR spectroscopy since it was assumed that they may be as unstable as pyrroloimidazolones. The NMR spectra showed that pyrrolo[1,2-*a*]benzimidazol-1-ones were the only products of pyrolysis although there were noticeable quantities of white insoluble polymeric material remaining in the U-tube trap after the soluble product had been rinsed out.

Large-scale preparative pyrolysis of **291** presented difficulties so several 100 mg scale pyrolyses were performed to optimise the process. The initial pyrolysis showed several areas that required attention. In the early stages of the pyrolysis, with low inlet temperature, a yellow pyrolysate was formed that was accompanied by a rise in pressure. As the precursor began to melt at the inlet the pyrolysis appeared to stop and the pressure returned to its previous lower level. Furthermore, the poor volatility of the substrate increased the duration of the pyrolysis and required elevated inlet temperatures for sublimation that resulted in some degradation of the substrate. When using a U-tube trap thermal degradation of the pyrolysate at the furnace exit occurred and is presumably due to the increased residence time at the furnace exit. To minimise loss of product as degradation material a dry ice/acetone cold-finger trap was employed to keep the pyrolysate cold for the duration of the pyrolysis.

These conditions met with some success although some material continued to condense at the furnace exit and degrade despite wrapping the furnace exit/trap inlet in foil to keep it warm and force condensation on to the cold-finger. The duration of the pyrolysis could be shortened by increasing the inlet temperature therefore increasing the rate of precursor sublimation but this lead to more precursor degradation and large increases in the formation of the white polymeric side-product. Ideal conditions for a half gram pyrolysis of **291** were found to involve a long duration (105 min) with low inlet temperature (115 °C) such that the rate of melting was the same as the rate of sublimation, hence minimising precursor degradation and reducing the quantity of polymeric material formed, combined with a dry ice/acetone cold-finger trap with the furnace exit/trap inlet wrapped in foil to maximise the yield of **280** obtained (Scheme 84).

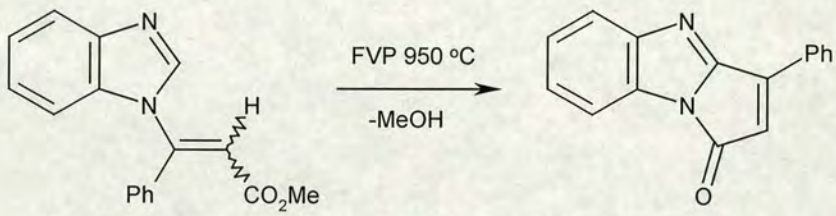


291 **280**

Scheme 84

Upon completion of the pyrolysis the products were washed from the cold-finger with dry ether under a dry nitrogen atmosphere. Fortunately the pyrrolo[1,2-*a*]benzimidazol-1-one **280** is more stable than its imidazole analogue **233** to such an extent that purification by dry flash chromatography was possible although it was found that a very polar eluent system was required (70% ethyl acetate in hexane) and that the isolated product had to be recovered from the column within 5 min. Such specific chromatographic requirements were crucial since **280** is easily lost as degradation material if left absorbed onto silica for too long. However, the crude pyrolysate did not contain much impurity and pure **280** was recovered as the first fraction in 71% yield.

The large scale preparative pyrolysis of **293** presented the same problems as encountered in the pyrolysis of **291**. The conditions for FVP of **291** were used to achieve the maximum yield of the 3-phenylpyrrolo[1,2-*a*]benzimidazol-1-one **295** possible, the only change being that the inlet temperature was increased from 50 °C to 180 °C during the course of the pyrolysis to maintain the rate of sublimation of **293**. Despite the use of the cold-finger trap and wrapping of the furnace exit/trap inlet in foil, the vast majority of product condensed at the furnace exit rather than on the cold-finger itself. Consequently there was a large degree of thermal degradation during the pyrolysis. No solution could be found to stop condensation at the furnace exit (Scheme 85).



293 **295**

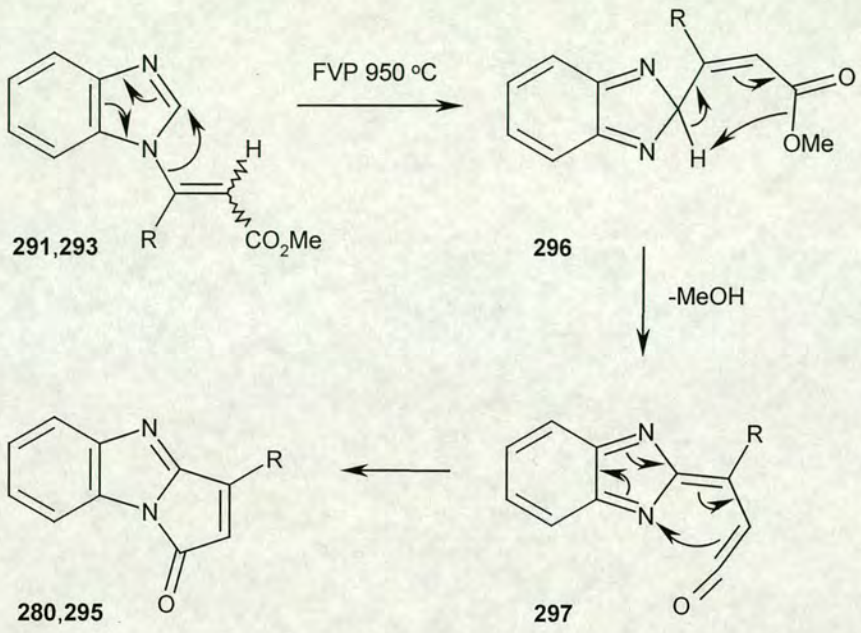
Scheme 85

The pyrolysate was washed from the trap with dry ether under a dry nitrogen atmosphere as before and absorbed onto silica for immediate chromatographic separation on a pre-prepared dry flash column with 50% ethyl acetate in hexane. The 3-phenylpyrrolo[1,2-*a*]benzimidazol-1-one **295** was recovered in the first fraction and the solvent removed at the oil pump to afford pure **295** in 36% yield.

2.2.4 Mechanism and scope of azabenzopyrrolizin-1-ones synthesis by FVP of benzimidazole *N*-propenoate precursors

Importantly the rearrangement FVP strategy has, for the first time, allowed ready access to pyrrolo[1,2-*a*]benzimidazol-1-ones. The previously unreported parent compound **280** can be obtained in just two steps and in 68% overall yield from readily available starting materials. The mechanism of pyrrolo[1,2-*a*]benzimidazol-1-one formation is as discussed in section 2.1.1 (Scheme 62) with the only difference being that the initial migration of the propenoate from nitrogen to carbon involves

the formation of a quinonoid system. Elimination of methanol and electrocyclisation follow to generate the pyrrolo[1,2-*a*]benzimidazol-1-one products (Scheme 86).



Scheme 86

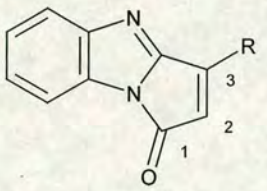
The furnace temperature of 950 °C used for pyrolysis is approximately 100 °C higher than that used for any pyrolyses of pyrroloimidazolone precursors where the (*E*)/(*Z*) isomerisation of the propenoate occurs at temperatures between 650-850 °C[48] and the migration occurs at around 850 °C. The furnace higher temperature is necessary to break the aromaticity of the benzene ring during the migration step in the generation of the 2*H*-benzimidazole propenoate intermediate **296** and to maintain the quinonoid system during the elimination of methanol to form the ketene intermediate **297**. Rapid restoration of aromaticity drives electrocyclisation to form the lactam (Scheme 86).

Some further optimisation of pyrolysis conditions would doubtlessly be possible to increase the yields, particularly of the phenyl derivative **295**, since it is the apparatus itself that is limited and not the process, which is potentially general. The use of a diffusion pump to generate much lower pressure in the system may be beneficial as it would lower the required inlet temperature for sublimation therefore reducing

precursor degradation and may potentially shorten the duration of the pyrolysis and hence loss of product through thermal degradation. The lower pressure may also encourage condensation of **295** on the cold-finger surface instead of at the furnace exit.

2.2.5 Spectroscopic properties of azabenzopyrrolizin-1-ones

The azabenzopyrrolizin-1-ones **280** and **295** were characterised by ^{1}H NMR, ^{13}C NMR and mass spectroscopy. Little assignment of proton and no assignment of carbon resonances have been performed since it is not possible to assign fully resonances of pyrrolo[1,2-*a*]benzimidazol-1-one by NOE data. The compounds are both bright yellow in colour like the pyrroloimidazol-5-one analogues due their extensive conjugation.



Since no coupled NMR spectra were recorded the only proton assignments possible are those of the enone protons. In **280** the H-2 and H-3 proton resonances occur at δ_H 6.27 ppm and δ_H 7.24 ppm respectively. The H-3 resonance has a similar chemical shift to the H-7 (same relative position in the ring system) resonance of the pyrroloimidazol-5-one analogue **233** but the H-2 resonance is shifted to higher frequency relative to its **233** equivalent by $\Delta\delta_H$ 0.3 ppm, presumably as a consequence of the stronger conjugative electron withdrawal effect of benzimidazole relative to imidazole. The H-2 resonance at δ_H 6.43 ppm of **295** shows the same shift, $\Delta\delta_H$ 0.3 ppm, to higher frequency relative to its pyrroloimidazol-5-one analogue **248**.

The mass spectra of **280** and **295** show weak molecular ions (M^+) of typically 30-35% intensity. A much stronger signal is observed at for the loss of CO (M^+ -28). The fragmentation patterns follow no discernable order and are of low intensity.

The infra-red spectra of **280** and **295** show strong carbonyl bands at 1748 cm^{-1} and 1747 cm^{-1} respectively. These carbonyl bands are at remarkably high frequency and are consistent with a lack of normal amide type delocalisation but are typical of the carbonyl stretching frequency observed in the analogous pyrrolo[1,2-*a*]imidazol-5-one **233** and pyrrolo[1,2-*c*]imidazol-5-one **234** systems (1760 cm and 1750 cm respectively).[48]

2.3 Formation of benzo[1,2-*a*]pyrrolizinones

2.3.1 Introduction

The synthesis of benzo[1,2-*a*]pyrrolizinones has been reviewed in section 1. Benzopyrrolizinone is a generic term to describe the ring system and is used when making general points. Specific benzopyrrolizinone products are named using the formal systematic nomenclature, for example the parent benzopyrrolizinone has the systematic name pyrrolo[1,2-*a*]indol-3-one **2**.

The preparation of benzo[1,2-*a*]pyrrolizinones under flash vacuum pyrolysis conditions has previously been carried out using Meldrum's acid derivative precursors.[19,20] However, whilst the pyrolysis step itself is clean and high yielding, the route does have limitations. Firstly, the starting material for the precursor of the parent compound **2** is 2-formylindole before condensation with Meldrum's acid. Literature methods often begin with indole 2-carboxylic acid, and selective reduction requires several steps, besides which very few substituted indole 2-carboxylic acids are readily available to allow a variety of precursors to be made.[21] The starting materials for the precursors of 9-substituted benzopyrrolizin-3-ones are 3-substituted indole 2-carbaldehydes. Though these can be obtained in low yield *via* Vilsmeier reactions of 3-substituted indoles under forcing conditions, they usually require chromatographic separation of the desired product from the 3-substituted indole *N*-carbaldehyde side-product and recovered starting material.[20] Secondly, no 2-substituted benzo[1,2-*a*]pyrrolizinones can be obtained *via* this route since during pyrolysis the initially generated methyleneketene intermediate **80** has to undergo a [1,7] hydrogen shift to form the ketene **81** before electrocyclisation to the product (section 1.1.2.3.3, Scheme 11).

This section describes the expansion of the flash vacuum pyrolysis technique that utilises the thermal rearrangements of indole 3-propenoate and indole *N*-propenoate precursors for benzo[1,2-*a*]pyrrolizinone synthesis.

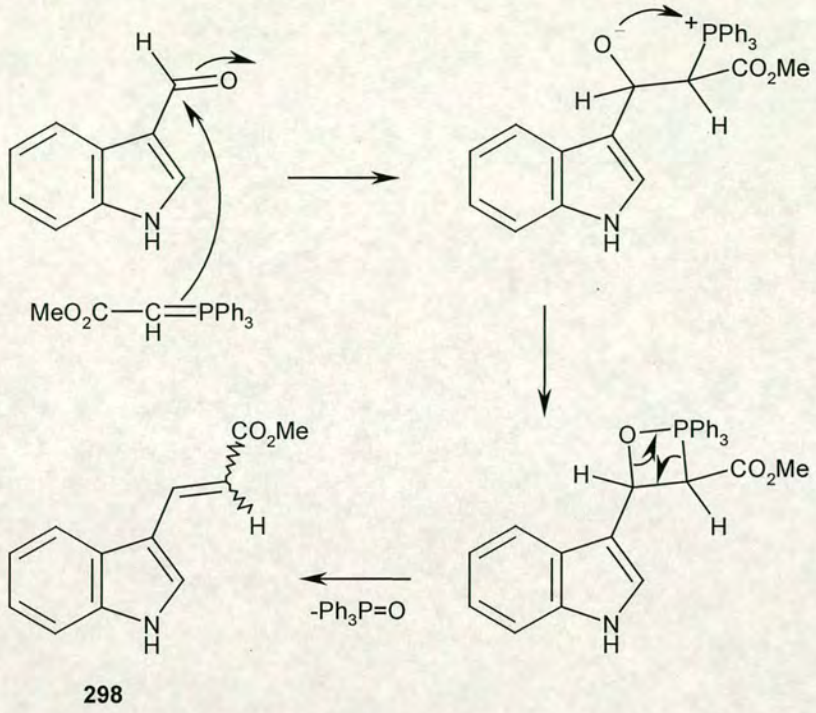
2.3.2 Preparation of precursors

A range of propenoate precursors was prepared to investigate the scope of benzopyrrolizinone synthesis by the rearrangement FVP route.

2.3.2.1 Preparation of indole 3-propenoate precursors

Benzimidazole was found to be highly reactive with propynoic acid methyl ester in the generation of the benzimidazole *N*-propenoate precursor **291** due to the presence of a non-delocalised nitrogen lone-pair that was available for nucleophilic attack at propynoic acid methyl ester. Indole does not have such a lone-pair and as a result is much less reactive towards conjugate addition at the β-carbon of propynoic acid methyl ester. For this reason the first series of benzopyrrolizinone precursors synthesised were indole 3-propenoates, rather than indole *N*-propenoates, since these could more readily obtained *via* Wittig/Knoevenagel type reactions of indole 3-carboxaldehyde with an active methylene compound.

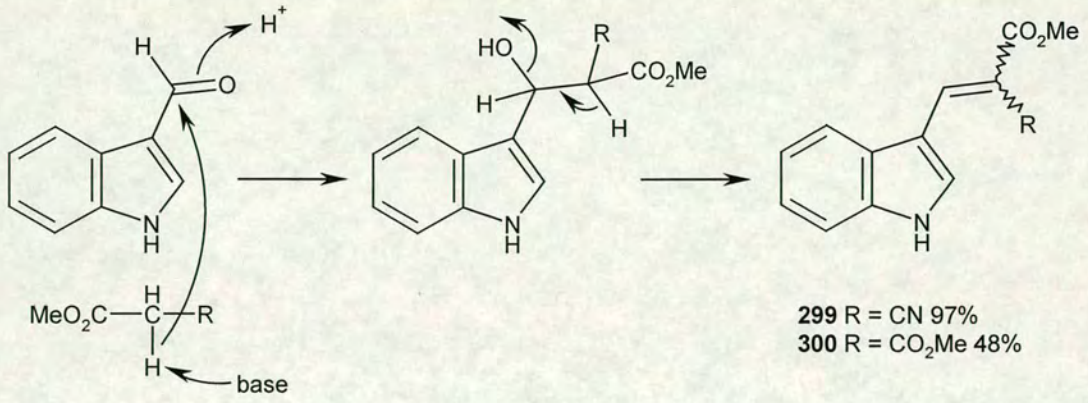
The precursor **298** was prepared by the reaction of indole 3-carboxaldehyde with methyl (triphenylphosphoranylidene) acetate in toluene. Stirring overnight and removal of the solvent *in vacuo* afforded crude **298** as a 90:10 mixture of (*E*)- and (*Z*)-isomers that were identified by the coupling constants of the propenoate C-2' and C-3' protons in the ^{1}H NMR spectrum. Purification by dry flash column chromatography removed the triphenylphosphine oxide side-product and gave separation of the (*E*)- and (*Z*)-isomers of **298** in 88% overall yield with no change in the isomeric ratio (Scheme 87).



298

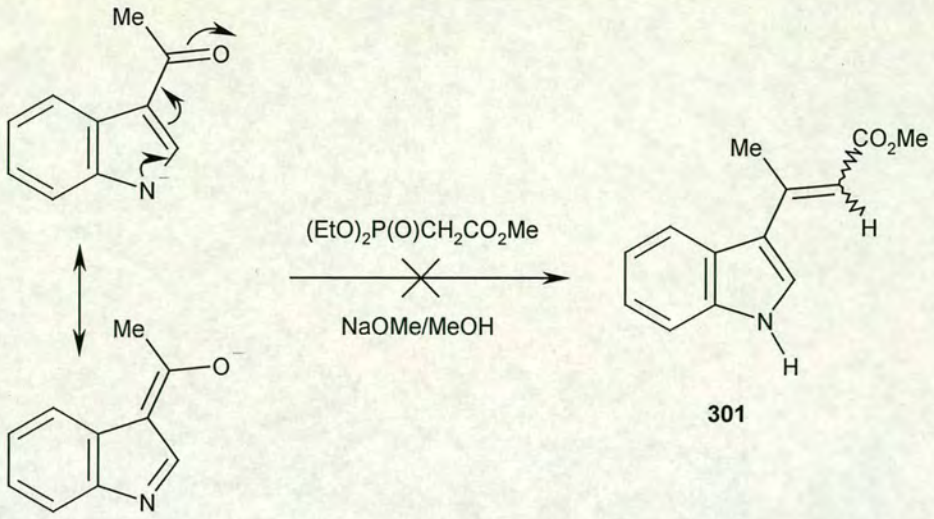
Scheme 87

The 2'-substituted indole 3-propenoates **299** (R = CN) and **300** (R = CO_2Me) were prepared by treatment of indole 3-carboxaldehyde with an active methylene compound (methyl cyanoacetate for **299** or dimethyl malonate for **300**) in the presence of glacial acetic acid and piperidine in toluene. The reaction of indole 3-carboxaldehyde with methyl cyanoacetate occurred readily at room temperature over 2 h and afforded **299** in 97% yield, whereas the reaction with dimethyl malonate to give **300** required heating under reflux with a Dean/Stark trap for 2 h and gave only 48% yield. This may be a consequence of the marginally higher stability of the methyl cyanoacetate anion, due to the stronger electron withdrawing effect of the cyano group, relative to that of the dimethyl malonate anion as well as the greater steric bulk associated with the presence of two methyl ester groups rather than one. Extraction with DCM or ether and removal of the solvent afforded the pure precursors **299** and **300** (Scheme 88).



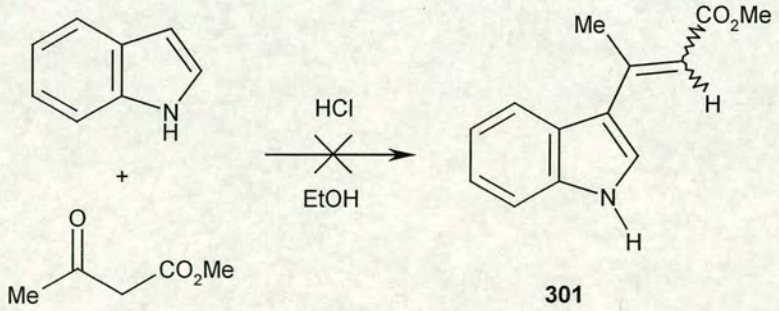
Scheme 88

In order to introduce a substituent at the propenoate C-3' position a Wittig-Horner reaction of 3-acetylindole with methyl diethylphosphonoacetate was attempted to obtain **301**. Methyl diethylphosphonoacetate was added to a solution of sodium methoxide and stirred for 30 min after which a solution of 3-acetylindole in methanol was added dropwise. The reaction was heated under reflux for 48 h then extracted with ether. A proton NMR spectrum of the organic products showed that only recovered 3-acetylindole was present. It is likely that this reaction failed due to the indole nitrogen proton being more acidic than the phosphonate since the anion is stabilised by conjugation of the nitrogen lone pair with the carbonyl moiety (Scheme 89).



Scheme 89

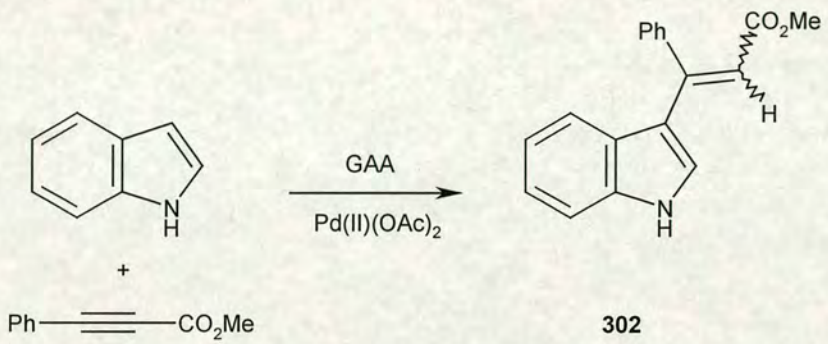
A literature preparation was found in which the reaction of indole with methyl acetoacetate under acidic conditions leads in one step to the precursor **301**.[79] the reagents were added together and the reaction left to stand overnight during which time it became deep red in colour. The organic products were extracted with ether then analysed by proton NMR and mass spectroscopy. Not surprisingly no single identifiable product was obtained (Scheme 90).



Scheme 90

Having failed to introduce a methyl substituent to the C-3' position of the propenoate, another literature method was found involving the addition of pyrrole to methyl phenylpropiolate by palladium catalysis to give a pyrrole substituent in the propenoate C-3' position.[80,81] A test reaction using pyrrole with 2% palladium acetate

catalyst in glacial acetic acid afforded the 3-(pyrrol-2-yl)-3-phenylpropenoate in 69% yield. The same methodology was applied to the reaction of methyl phenylpropiolate with indole. Both reagents were added together in glacial acetic acid with 2% palladium acetate and stirred at room temperature for 30 h. The crude product was then purified by dry flash chromatography to afford a 89% yield of 3-(indol-3-yl)-3-phenylpropenoate precursor **302** as a 90:10 *E/Z* isomer mixture (Scheme 91).



Scheme 91

It was not clear at which position the substitution had occurred. A proton NMR spectrum showed a broad NH signal and was lacking either a C-2 or C-3 proton resonance hence substitution at the indole nitrogen could be discounted. However, a NOESY NMR experiment was required to establish whether the reaction had taken place at the indole at the C-2 or C-3 position.

Correlation of the ester methyl resonance at δ_H 3.70 ppm with a one proton singlet at δ_H 6.62 ppm and a five proton multiplet at δ_H 7.32-7.40 ppm allowed assignment of the resonances as the propenoate H-2' proton and phenyl protons respectively. Both the phenyl and H-2' proton resonances showed a correlation with the characteristic indole H-4 aromatic proton resonance at δ_H 7.83 ppm therefore showing that the reaction had occurred at the indole C-3 position as desired.

Correlation of the propenoate H-2' proton at δ_H 6.62 ppm (and a lack of correlation of the ester methyl singlet at δ_H 3.70 ppm) with the indole H-4 proton at δ_H 7.83 ppm suggested that the major isomer was the (*E*)-isomer.

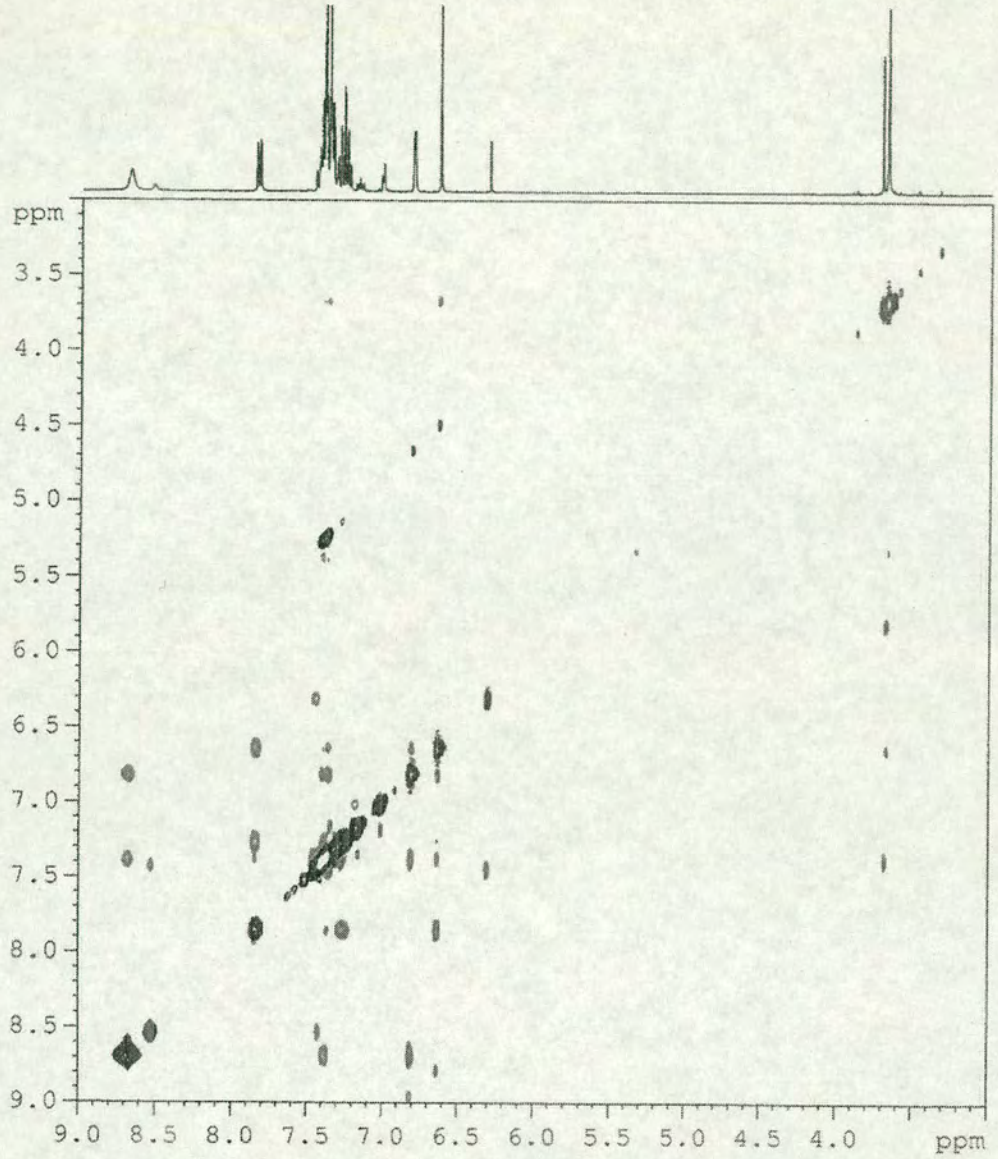


Figure 2 - ^{1}H NMR spectrum (360 MHz) and NOESY spectrum of precursor **302**

Final confirmation of the product as **302** was obtained from the crystal structure as shown in Figure 3 which clearly shows that the addition of the alkyne has occurred at the indole 3-position.

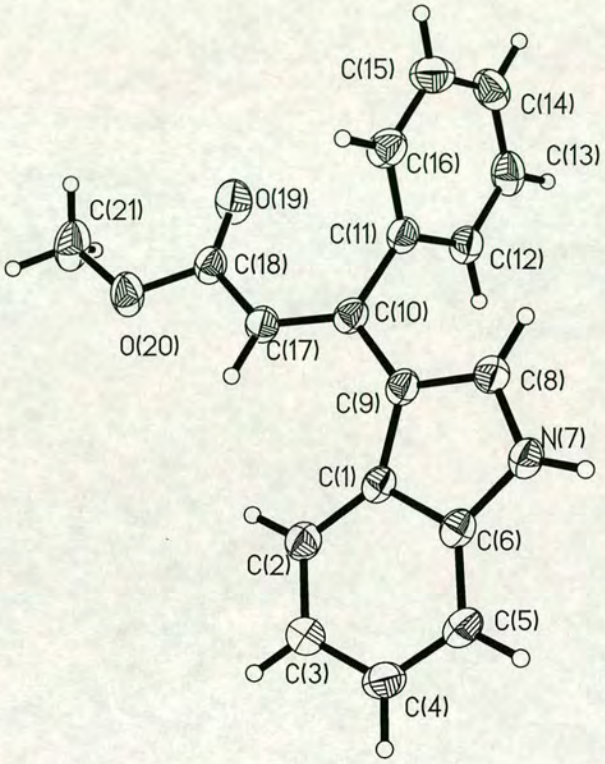
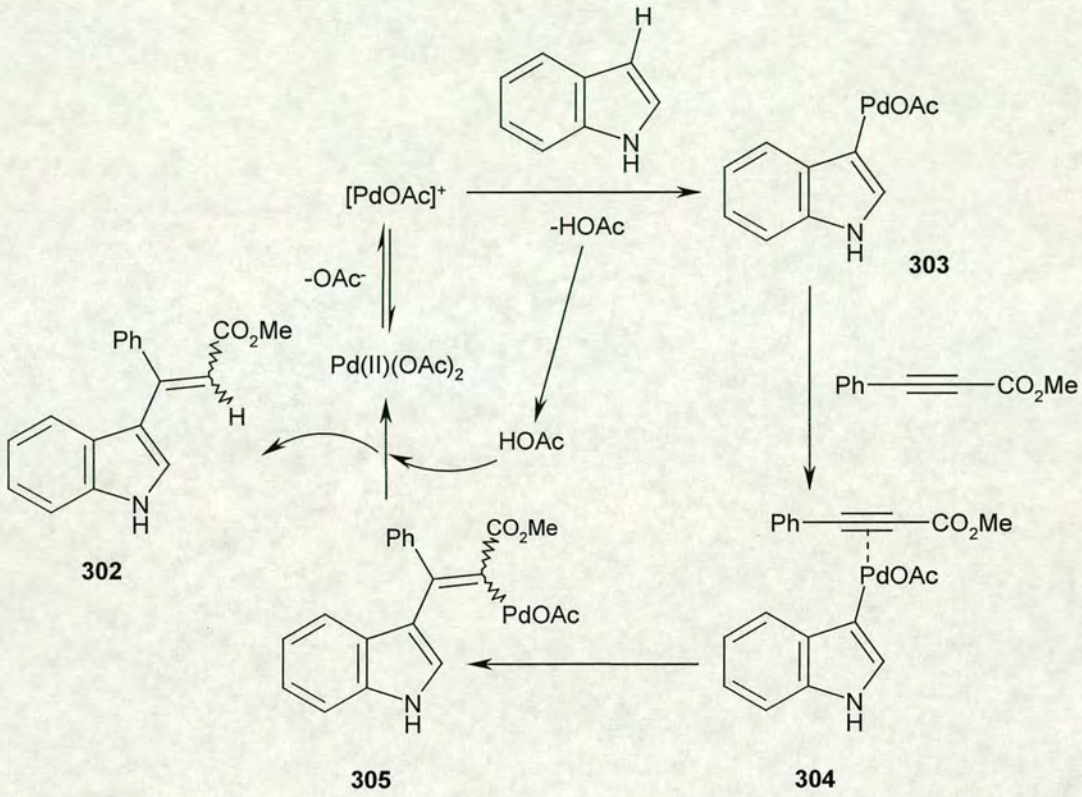


Figure 3 - crystal structure of precursor **302**

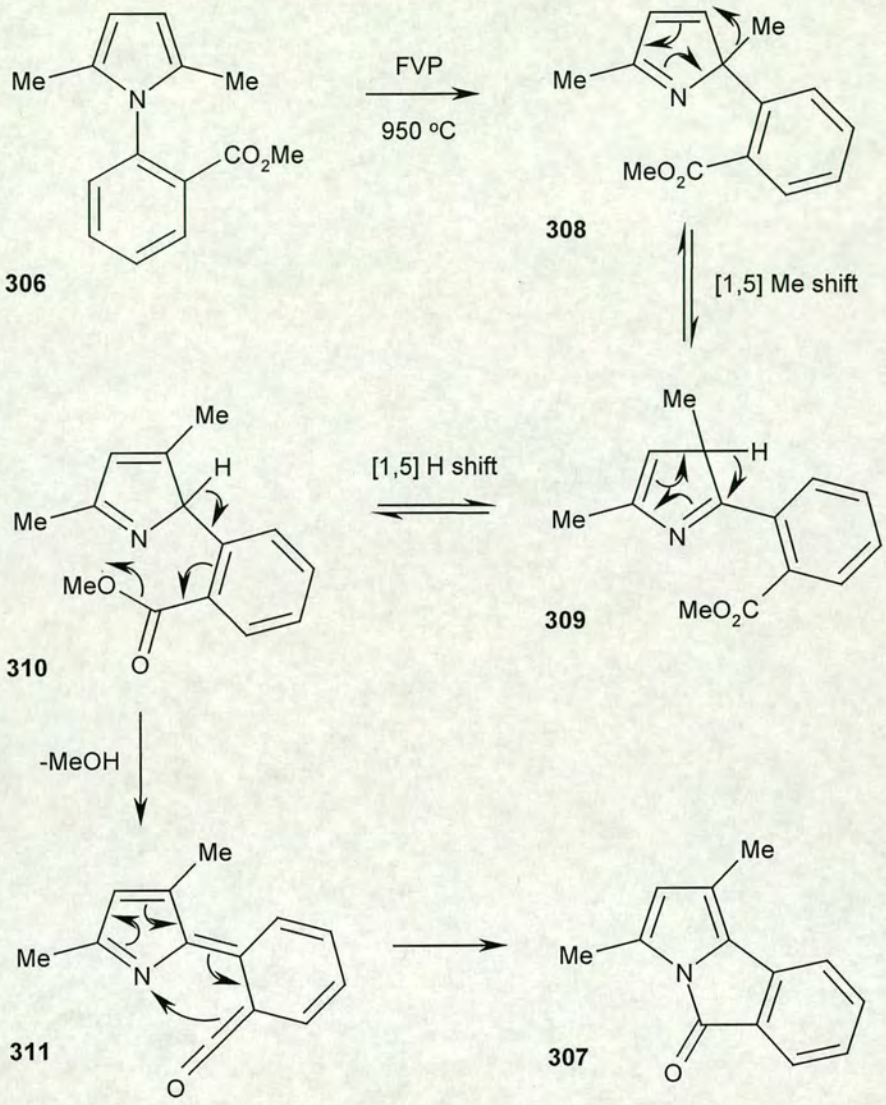
A possible mechanism for the reaction has been suggested by Fujiwara *et al* and involves electrophilic substitution of the most active aromatic proton by a cationic palladium(II) species that results in the formation of a σ-arylpalladium complex **303**. Coordination with the methyl phenylpropiolate affords **304** after which insertion of the carbon-carbon triple bond to the σ-aryl-palladium bond gives the vinyl complex **305**. Upon protonation of **305**, compound **302** is released from the palladium(II) species which is regenerated for further cycles (Scheme 92). The presence of the acid is likely to facilitate both the formation of the cationic palladium(II) species and the protonation of the vinyl-palladium complexes. Indeed the rate of reaction is

increased 20-fold when acid is used instead of other solvents such as water, chloroform and ether.[81]



Scheme 92

As previously stated, it is thought that under FVP conditions, sigmatropic shifts by carbon-to-carbon migrations are reversible.[58] It has been shown that under FVP conditions, at 950 °C, 2,5-dimethyl-1-(2-carbomethoxyphenyl)pyrrole **306** gives 1,3-dimethylpyrrolo[2,1-*a*]isoindolo-5-one **307**. The mechanism of formation probably involves a nitrogen-to-carbon migration of the aryl group to give **308** followed by a carbon-to-carbon migration of the methyl substituent affording **309** and a subsequent [1,5] hydrogen shift to give **310** before elimination of methanol forms the ketene **311** that undergoes electrocyclisation to the product **307** (Scheme 93).[82]

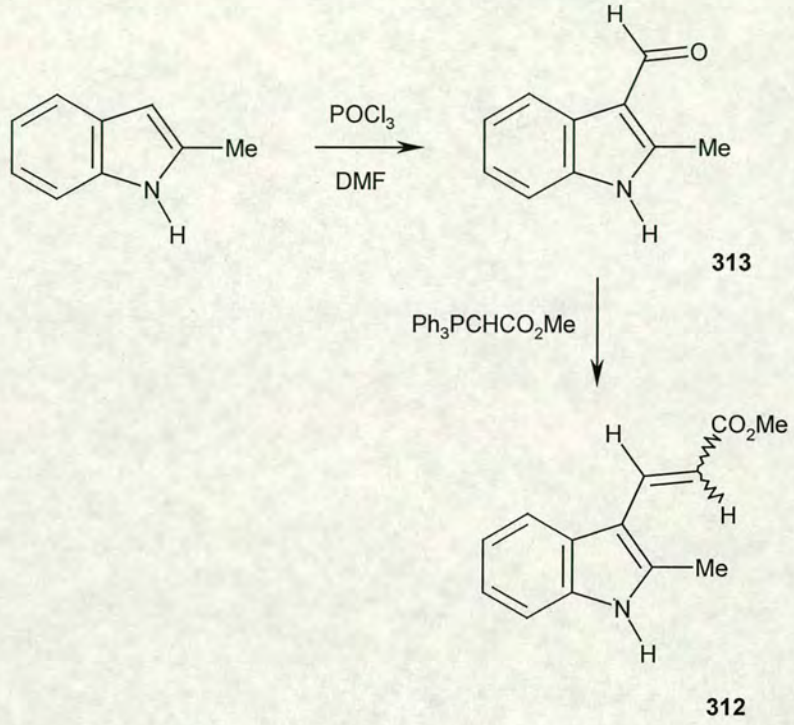


Scheme 93

From the result above it could be envisaged that 9-methylpyrrolo[1,2-*a*]indol-3-one **78** may be formed by pyrolysis of the 2-methyl-3-propenoate indole precursor **312**. The methyl and propenoate groups could effectively swap position on the indole upon pyrolysis and since it is the migration step itself that is the rate determining step then rapid cyclisation to the benzopyrrolizinone product **78** may drive the rearrangement.

The precursor **312** was obtained from a Vilsmeier formylation of 2-methylindole under standard conditions (section 3.5.1) to give 2-methyl-3-formylindole **313**

followed by a Wittig reaction of the crude aldehyde with methyl (triphosphoranylidene) acetate. Purification by dry flash chromatography afforded **312** in 75% overall yield (Scheme 94).



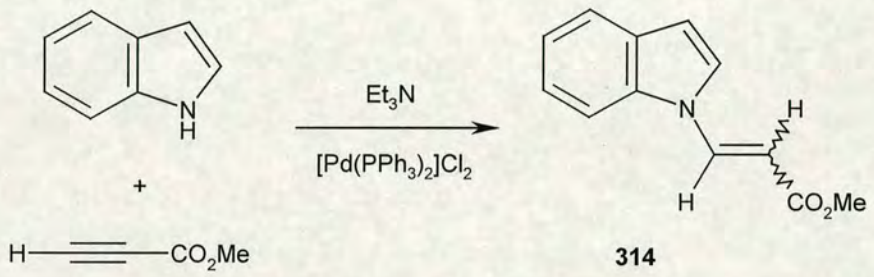
Scheme 94

2.3.2.2 Preparation of indole *N*-propenoate precursors

The series of indole 3-propenoate precursors have one major disadvantage. Since the propenoate group occupies the indole 3-position of the precursor then any substituent of a 9-substituted benzopyrrolizinone must be introduced by the proposed C-2 to C-3 migration mechanism. Relatively few 2-substituted indoles are available and hence the route is not general. However, indole *N*-propenoate precursors do offer access to such substituted benzopyrrolizinones since there is no mechanistic requirement for 3-position substitution. For this reason efforts were made to synthesise a series of indole *N*-propenoate precursors.

The initial experiments were focused upon synthesis of the benzopyrrolizin-3-one parent precursor **314** based on a literature method in which indole was reacted with a propynoate in the presence of a palladium catalyst.[83]

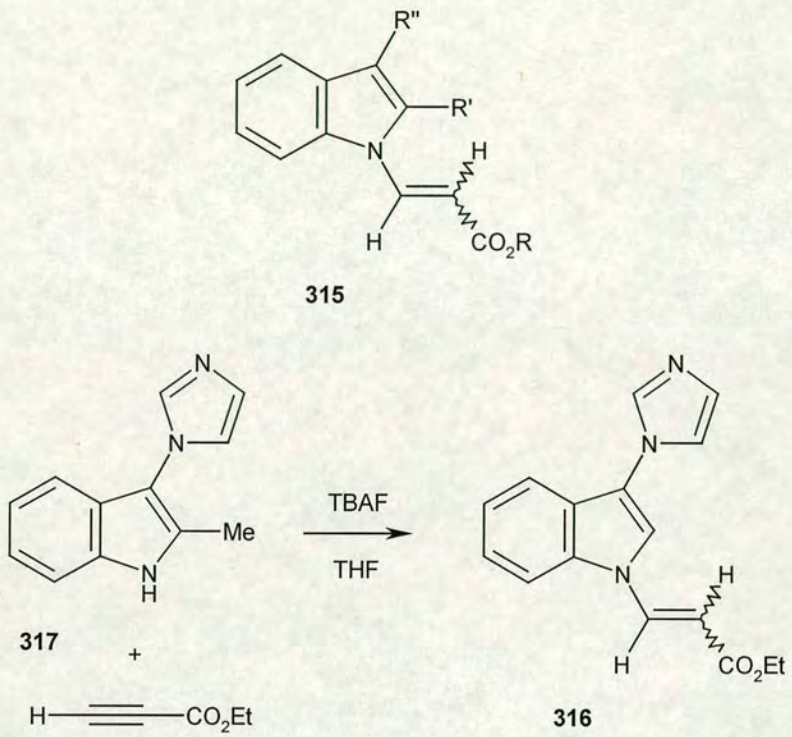
Indole and *trans*-dichlorobis(triphenylphosphine)palladium (II) (2%) were added together in triethylamine under a nitrogen atmosphere with light protection. Methyl propiolate was added dropwise with stirring and the reaction heated under reflux overnight. Removal of triethylamine *in vacuo* and purification by dry flash chromatography afforded the indole *N*-propenoate precursor **314** in 25% yield as a 76:24 mixture of (*E*)- and (*Z*)-isomers respectively where structures were assigned on the basis of the olefinic proton coupling constants in the ^{1}H NMR spectrum (Scheme 95).



Scheme 95

Upon addition of the methyl propiolate the reaction quickly changed from a colourless solution and became dark brown in colour. This is possibly due to an immediate reaction of methyl propiolate with the large excess of triethylamine present. A second reaction was performed using a largely reduced volume of triethylamine and a 2-fold excess of methyl propiolate in order to begin to optimise the yield of **314**. However, the same immediate colour change was observed and after work-up only a 31% yield of product was obtained and it became apparent that the reaction was unviable hence another route to **314** was sought. It is not clear what mechanistic role the palladium catalyst fulfils in the reaction if any at all. There are no other reported instances in which a palladium (II) catalyst has been used in a reaction of the hetero atom of a nitrogen heterocycle with a propynoate carbon-carbon triple bond.

Although **314** has only been made by the palladium catalysed route outlined above, a complete search of the substructure **315** revealed that **316** had been made by conjugate addition of indole **317** to ethyl propiolate (Scheme 96).[84]

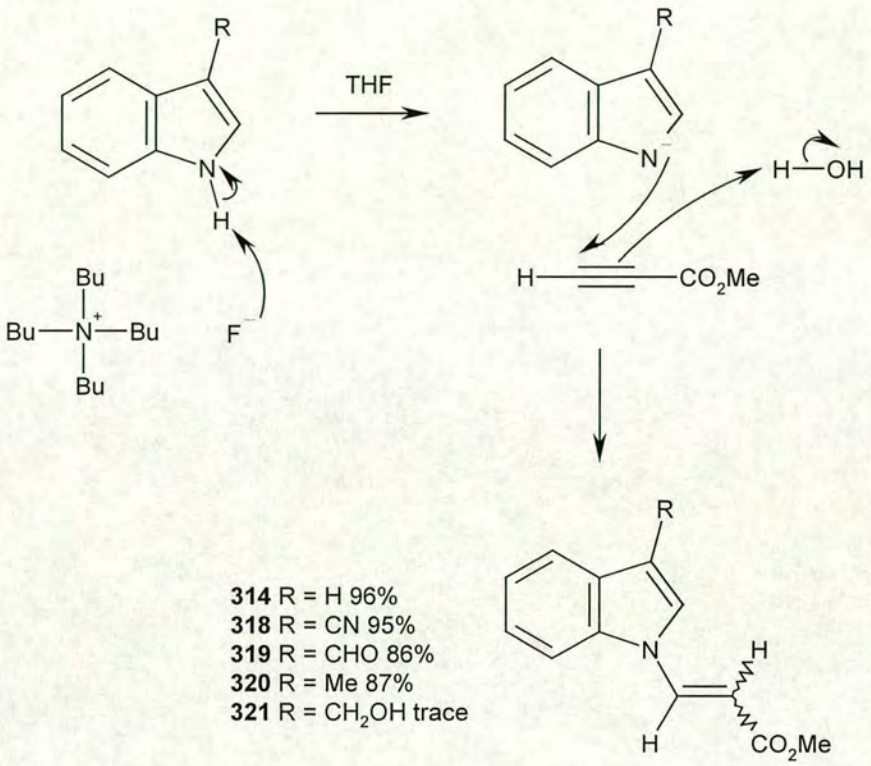


Scheme 96

The choice of base is critical in this reaction; benzyltrimethylammonium hydroxide gave low yields of **316** with much tarry material whereas the addition is successful when using tetrabutylammonium fluoride giving **316** in 52% yield.[84] This procedure was found to be general and was used to synthesise a range of indole *N*-propenoate precursors **314** and **318-320**.

Equimolar amounts of the indole and methyl propiolate were added together in tetrahydrofuran. A molar equivalent of a 1 M solution of tetrabutylammonium fluoride in THF was added dropwise at room temperature and the reaction allowed to stir for 30 min after which removal of the solvent afforded the crude indole *N*-propenoate. Purification by distillation, recrystallisation or dry flash chromatography gave the precursors in yields of 86-96% (Scheme 97). This method is clearly

advantageous over the palladium route (Scheme 95) since it is quicker, cleaner and much higher yielding.



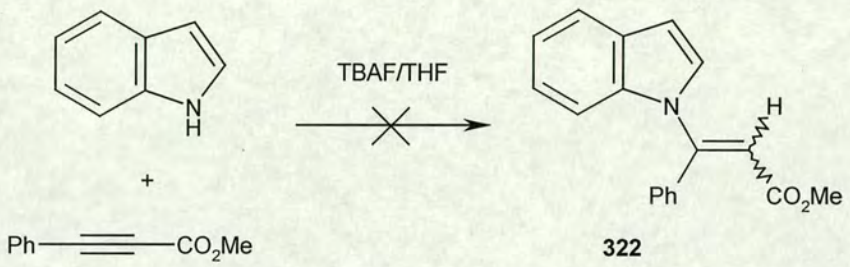
Scheme 97

The reaction between the indole and alkyne occurs readily at room temperature. The tetrabutylammonium fluoride base deprotonates the indole nitrogen to afford the anion that undergoes conjugate addition to the alkyne. The base is not catalytic and in an experiment involving a 2-fold excess of indole over tetrabutylammonium fluoride only a 48% yield was obtained. This suggests that the HF generated is not responsible for the protonation of the α-carbon, which must therefore be by small quantities of water in the THF solvent (Scheme 97).

The reaction with 3-hydroxymethylindole was unsuccessful. T. L. C. analysis indicated four major components in the reaction products but the proton NMR spectrum showed that only trace amounts of the 3-hydroxymethyl indole *N*-propenoate **321** were present so separation and identification of the components was

not performed. The reaction may have failed because of reaction between the alcohol moiety and the tetrabutylammonium fluoride base.

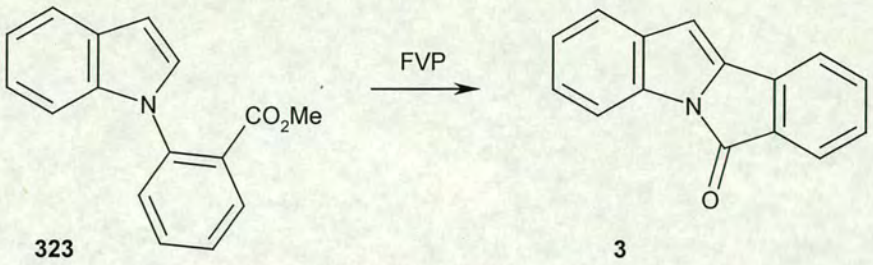
A similar reaction of indole with methyl phenylpropiolate instead of methyl propiolate under the same conditions gave no indole *N*-3-phenylpropenoate product **322** after stirring at room temperature for 4 h or after heating under reflux (Scheme 98). The failure of this reaction is probably a combination of steric hindrance between the indole and the phenyl moieties and the electronic deactivation of the alkyne bond to addition of indole by conjugative electron donation from the phenyl group.



Scheme 98

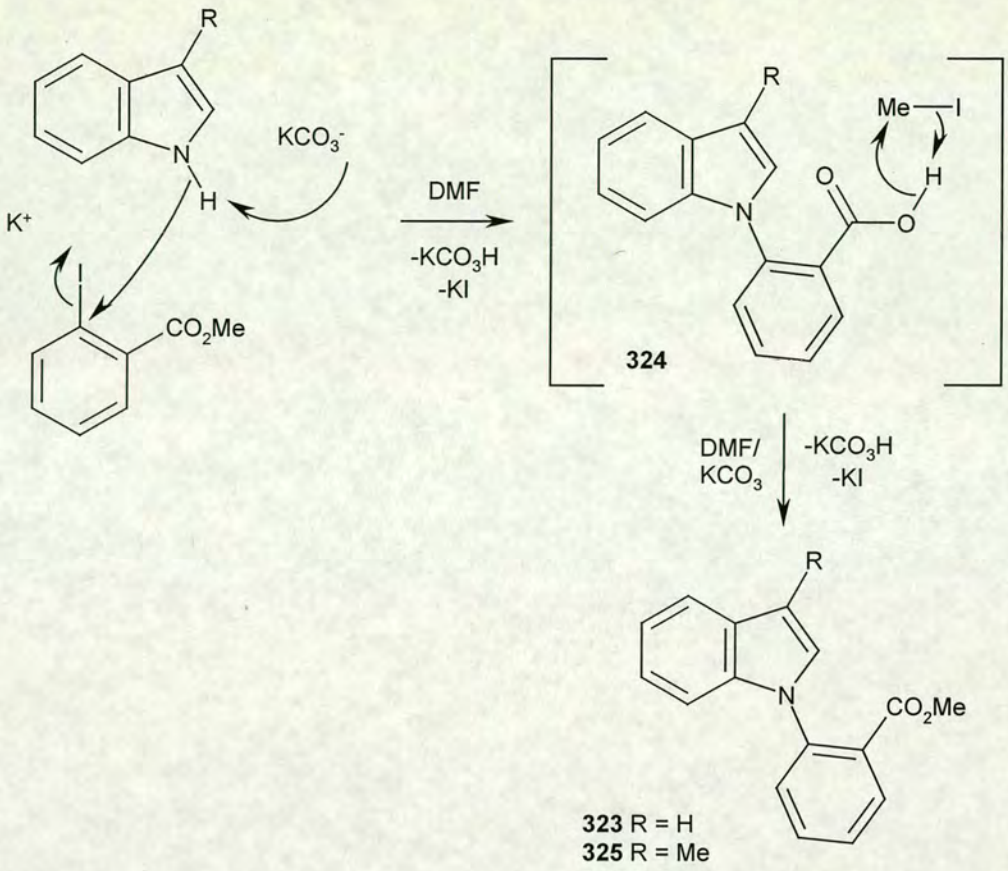
2.3.2.3 Preparation of indole *N*-benzoate precursors

Under the rearrangement FVP conditions it can be envisaged that replacement of the propenoate substituent of **314**, with a benzoate substituent **323**, may lead to formation of the bis-annulated derivative of pyrrolo[1,2-*a*]indol-3-one **2**, the known tetracycle isoindolo[2,1-*a*]indol-6-one **3** (Scheme 99).



Scheme 99

The precursor **323** was synthesised in two step in a 'one-pot' reaction. A suspension of indole, 2-iodobenzoic acid and a 2-fold excess of anhydrous potassium carbonate was heated under reflux in DMF for 48 h to generate the indole *N*-benzoic acid **324**. This product was not isolated but rather esterified by treatment with an equivalent of methyl iodide and a second 2-fold excess of anhydrous potassium carbonate and stirred at room temperature for 48 h to give crude **323**. Extraction with ether and Kugelrohr distillation of the organic product afforded the pure indole *N*-benzoate **323** in 35% yield. The same preparative method was used for the synthesis of the 3-methylindole *N*-benzoate precursor **325**, obtained in 72% yield. This higher yield may be a result of blocking the potentially reactive 3-position with a mildly electron donating methyl substituent, enhancing the nucleophilic strength of the indole nitrogen lone pair (Scheme 100).



Scheme 100

2.3.2.4 Scope of precursor synthesis

The variety of syntheses used have allowed access to a range of indole propenoate precursors for benzopyrrolizin-3-one formation by flash vacuum pyrolysis. The range of precursors is useful for the identification of limitations in the FVP rearrangement process and as a source of various substituted benzopyrrolizin-3-ones for further functionalisation. The syntheses are generally one step processes from available starting materials and give good yields (generally >70%). The reactions with methyl propiolate involving tetrabutylammonium fluoride are particularly attractive from a synthetic perspective since they are complete in 30 min and are high yielding (86-96%) although in the absence of protecting groups this method does not appear to be general for all propynoates. Purification was achieved easily by dry flash column chromatography, recrystallisation or distillation. Whilst some precursors, *e.g.* **301** and **321**, were unobtainable in a single step it may be that lengthier syntheses, *e.g.* protection of the alcohol functional group in **321**, would

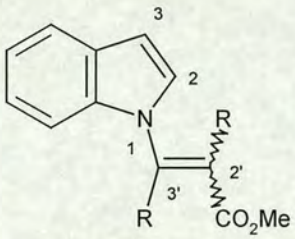
give access to many more precursors. Although the preparation of the indole *N*-benzoate precursors is time consuming, it is a 'one-pot' reaction with a simple distillation being all that is required to obtain pure material. No other literature precedent has been reported that offers a better synthesis.

2.3.3 Spectroscopic properties of benzopyrrolizin-3-one precursors

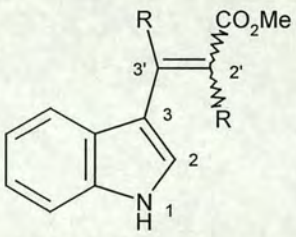
The indole precursors were all characterised by ^{1}H NMR, ^{13}C NMR and mass spectroscopy and by comparison with reported literature data. Where necessary accurate mass and/or elemental analysis was performed. No HSQC experiments were performed to allow assignment of carbon resonances.

2.3.3.1 ^{1}H NMR spectra

The resonances of the propenoate and pyrrole ring moieties of the indole propenoate precursors have been as fully assigned as possible and are listed according to the numbering scheme below (Tables 15 and 16).



R = H, **308**



R = H, **298**

The H-2 signals in the proton NMR spectra of the unsubstituted indole propenoates **298** and **314** are at significantly higher chemical shift than that of indole (δ_H 7.00 ppm) and this is a result of the close-in-space proximity of the ester moiety. The effect is most prevalent in the (*Z*)-isomers where the shift to higher frequency is up to $\Delta\delta_H$ 1.8 ppm whereas the shift in the (*E*)-isomers is only up to $\Delta\delta_H$ 0.3 ppm. The indole H-3 resonances of **314** are shifted little from those of indole (δ_H 6.50 ppm) and the coupling constants of the H-2 and H-3 protons are similar to that of indole (*J* 3.5 Hz).[60]

Precursor	Isomer	δ_H/ppm ($CDCl_3$)		
		H-2	H-2' (Hz)	H-3' (Hz)
298	*E*	-[a]	6.34 (*J* 15.7)	7.32 (*J* 15.7)
	Z	8.82	5.77 (*J* 12.4)	7.23 (*J* 12.4)
299	-[b]	8.57	---	8.55
300	---	8.16	---	7.77
302	*E*	6.79	6.62	---
	Z	-[a]	6.31	---
312	*E*	---	6.52 (*J* 15.8)	8.05 (*J* 15.8)

[a] – proton signal indistinguishable from other resonances with similar δ_H

[b] – geometry not established

Table 15 – Chemical shifts and coupling constants of 3-propenoate precursors

Precursor	Isomer	δ_H/ppm ($CDCl_3$)			
		H-2 (Hz)	H-3 (Hz)	H-2' (Hz)	H-3' (Hz)
314	*E*	7.30 (*J* 3.4)	6.67 (*J* 3.4)	5.90 (*J* 14.1)	8.24 (*J* 14.1)
	Z	8.46 (*J* 3.7)	6.58 (*J* 3.7)	5.32 (*J* 11.0)	-[a]
318	*E*	7.85	---	6.09 (*J* 14.2)	8.15 (*J* 14.2)
319	*E*	8.00	---	6.17 (*J* 14.4)	8.16 (*J* 14.4)
320	*E*	7.03	---	5.73 (*J* 13.9)	8.14 (*J* 13.9)

[a] – proton signal indistinguishable from other resonances with similar δ_H

Table 16 – Chemical shifts and coupling constants of *N*-propenoate precursors

The chemical shift values of the proton resonances of the propenoates **298-300**, **312** and **314**, **318-320** have been assigned by direct comparison with the imidazole and benzimidazole propenoate analogues (sections 2.1.3.1 and 2.2.2.1) and are broadly similar. For the precursor **314** the H-2' resonances are at lower frequency (up to $\Delta\delta_H$ 0.45 ppm) and the H-3' resonances are at higher frequency (up to $\Delta\delta_H$ 0.9 ppm)

relative to **298**. This may be a result of the increased opportunity for charge delocalisation in **298**.

The coupling constants of the *N*-propenoate olefinic resonances show very little variation compared with the corresponding imidazole and benzimidazole derivative precursors and so have been used to assign the geometry of the propenoates **314**, **318-320** whereas the 3-propenoate precursors **298** and **312** have larger coupling constant values (typically 2 Hz larger for each isomer) though have also been used to assign the propenoate geometry.

2.3.3.2 Mass spectra

The mass spectra of the precursors generally contain strong molecular ion (M^+) peaks with the only exception being the cyano precursor **299** (M^+ 38%). As in the mass spectra of other propenoates the fragmentation patterns all feature an initial loss of OMe (M^+ -31) followed by CO (M^+ -31 -28). Competing pathways of substituent loss complicate the spectra but all go to give a peak at *m/z ca.* 115-117 pertaining to indole species.

2.3.4 Flash vacuum pyrolysis

All the indole propenoate precursors were pyrolysed to give a range of benzopyrrolizinone products as yellow/orange solids. After removal of volatiles *in vacuo* the crude pyrolysates were analysed by proton NMR spectroscopy and in most instances were found to give the benzopyrrolizin-3-one as the sole product. However, in some pyrolyses side-products were generated and where possible were isolated. Some precursors failed to give the desired lactam products but these results are useful in defining the limitations of the process.

Large-scale preparative pyrolyses were subject to some problems. The furnace temperatures used during pyrolysis are over 900 °C but the products are not particularly volatile and condense at the exit point of the furnace and not 'round the bend' of the trap (section 3.2.9, Figure 14). Consequently the products are heated by radiant heat from the furnace causing some degree of thermal decomposition. Efforts

were made to minimise the loss of product through degradation by use of a cold-finger trap which is cooled with dry ice/acetone at -78 °C and can help to prevent thermal degradation of the product. However, in some pyrolyses the involatility of the products continued to cause condensation at the furnace exit. In an attempt to overcome this problem the furnace exit/trap inlet was lagged with foil in order to keep it hot and in doing so force a greater degree of condensation on the cold-finger surface but this precaution met with only limited success. The use of a diffusion pump to achieve lower pressure may promote condensation of the pyrolysate on the cold-finger surface.

Purification of the benzopyrrolizin-3-one products was generally achieved by dry flash chromatography since these compounds were found to be more stable on silica than the pyrroloimidazol-5-ones and pyrrolobenzimidazol-1-ones.

2.3.4.1 Flash vacuum pyrolysis of indole 3-propenoate precursors

Small-scale pyrolyses of the indole 3-propenoate precursors were performed for each precursor at temperatures of 850 °C, 900 °C, 925 °C and 950 °C to ascertain the optimum temperature for full conversion of the precursor into products and for all the precursors this was found to be 925 °C. This temperature is 50-100 °C higher than the furnace temperature used in the synthesis of pyrroloimidazol-5-ones (section 2.1.4) and is due to the need to break the aromaticity of not only the five-membered ring but the benzene ring too in the initial [1,5] hydrogen shift to form the *o*-quinonoid system so that the propenoate migration can occur (Scheme 101).

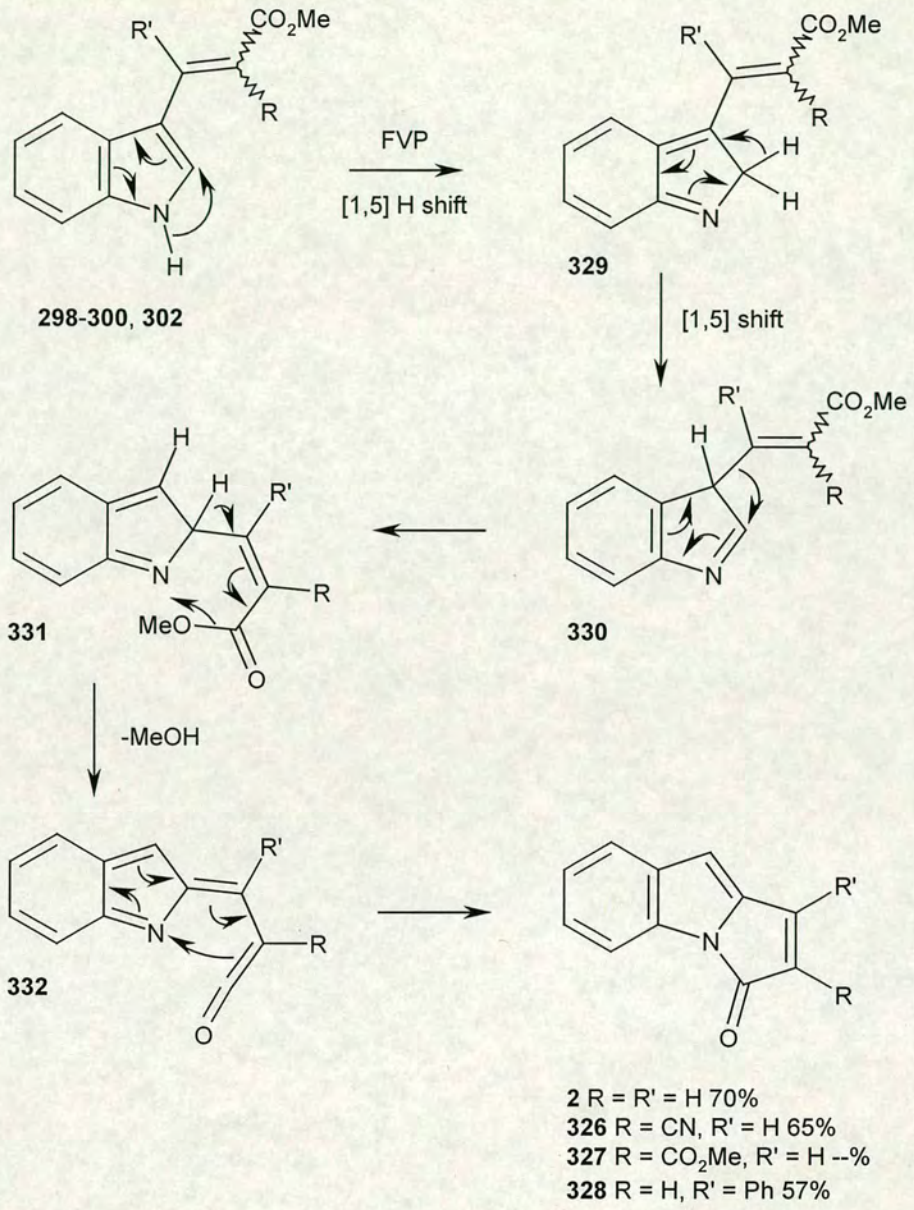
Initial large-scale pyrolysis (100 mg) of the parent precursor **298** proved problematic. The precursor melted at an inlet temperature of *ca.*110 °C and during this time small quantities of solid yellow pyrolysate were obtained in the trap. However, once melted the pyrolysis appeared to stop and a much higher inlet temperature of 210 °C was required to achieve full volatilisation over a period of 25 min. The liquid precursor became brown in colour from its initial colourless state indicating that degradation of the precursor was occurring and solid brown residues remained in the inlet tube upon completion of the pyrolysis. The use of a cold-finger trap proved

beneficial in keeping the pyrolysate cold for the duration of the pyrolysis and therefore preventing loss of product through thermal degradation at the furnace exit but no solution to the high inlet temperature requirement was found. However, the large-scale pyrolysis of **298** still afforded a respectable 70% yield of pyrrolo[1,2-*a*]indol-3-one **2** after purification of the crude product by dry flash chromatography.

The pyrolysis of the cyano derivative **299** was very similar to that of **298** although a high inlet temperature of 240 °C was used to volatilise a larger quantity of precursor (300 mg) in a shorter time period of 20 min. Residues were again present in the inlet tube upon completion of the pyrolysis and it seems that raising the inlet temperature in order to reduce the residence time at the inlet has little effect in the prevention of the degradation of the precursor. The crude product was washed off the cold-finger surface under a nitrogen atmosphere with acetone then immediately absorbed onto silica for purification by dry flash chromatography to give a 65% yield of 2-cyanopyrrolo[1,2-*a*]indol-3-one **326** (Scheme 101).

The pyrolysis of the dimethyl ester **300** proved unsuccessful. A yellow/brown oil was obtained and a proton NMR spectrum indicated that the only identifiable product was trace quantities of pyrrolo[1,2-*a*]indol-3-one **2**. The major components of the pyrolysate were decomposition products.

The mechanism of formation of the benzopyrrolizin-3-one products is very similar to that of the pyrrolizinones and azabenzopyrrolizinones. However, the initial migration is a [1,5] hydrogen shift to form the 2*H*-indole propenoate **329** followed by a second [1,5] hydrogen shift to generate **330** then migration of the propenoate group from the indole 3-position to the 2-postion occurs to afford the 2*H*-indole 2-propenoate **331**. The elimination of methanol is *via* extraction of the C-2 proton by methoxide, as in the mechanism of formation of **233**, **234** and **280** from 2*H*-azole propenoates, to generate the ketene **332** after which electrocyclisation gives the lactam products as previously seen (Scheme 101).



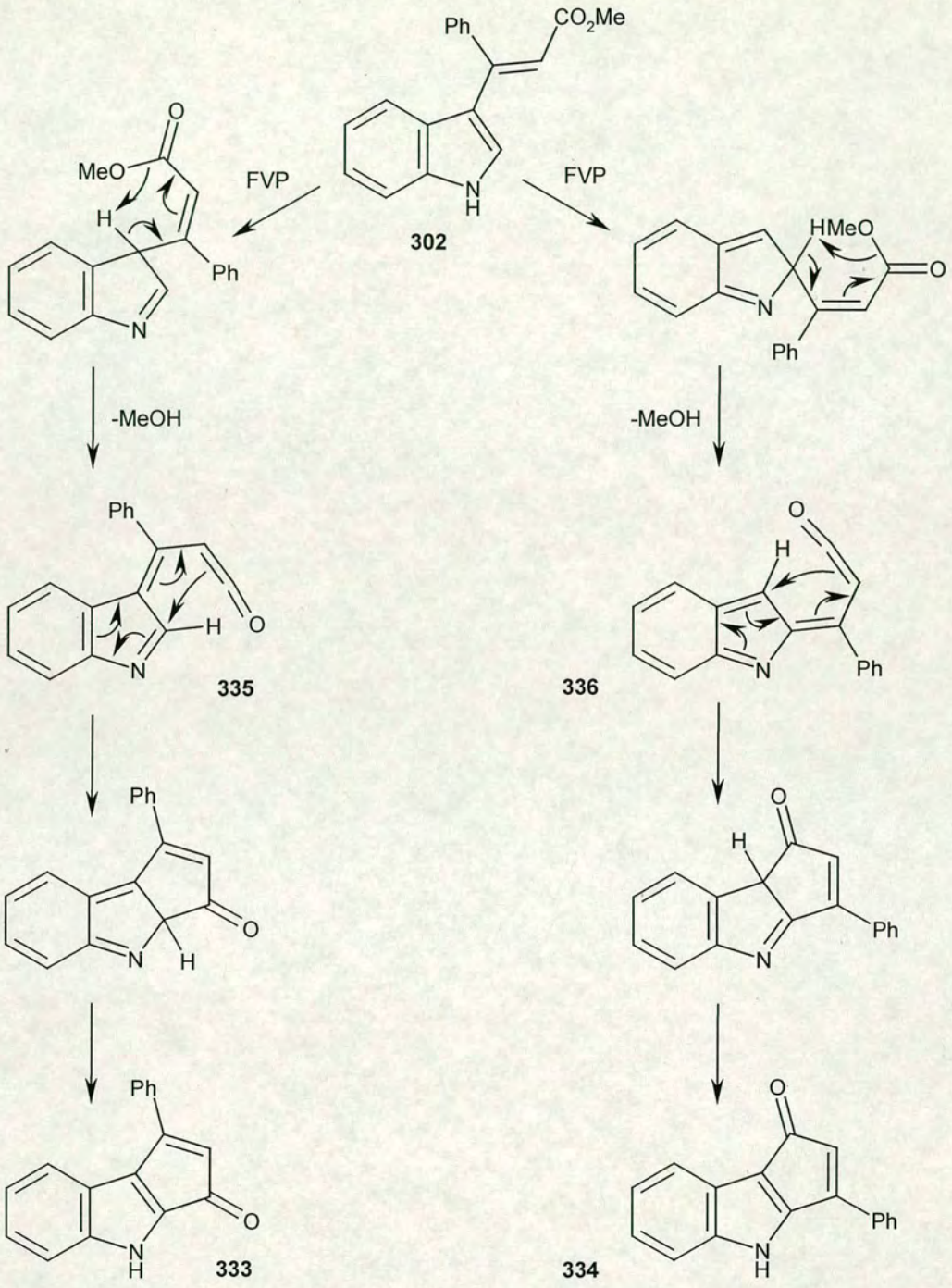
Scheme 101

The phenyl derivative **302** was pyrolysed under the same conditions as used for **298** but was much faster with full volatilisation of 120 mg of the precursor requiring only 8 min. Degradation of the precursor was less evident in this pyrolysis as had been observed in the pyrolysis of **298** and **299** but the pyrolysate collected at the furnace exit/trap inlet as well as on the cold-finger leading to loss of products through thermal degradation. The solid yellow pyrolysate that condensed on the cold-finger

was washed from surface and analysed by ^{1}H NMR spectroscopy and T. L. C. which both indicated two components in the pyrolysate. A dry flash column separation allowed each component to be isolated. The first product eluted from the column was the major component and was identified as 1-phenylpyrrolo[1,2-*a*]indol-3-one **328** and was obtained in 57% yield.

The second component was isolated in only 6% yield and was partially identified by NMR and mass spectroscopy. The proton NMR spectrum showed a broad NH signal at 11.44 ppm but no methine proton derived from the indole 3-position. Seven quaternary carbon and ten methine resonances were identified in the carbon NMR spectrum. The E.I. mass spectrum gave the molecular ion at *m/z* 245 and accurate mass gave the molecular formula as $C_{17}H_{11}NO$, the same as that of **328**, leading to identification of the second component as either 1-phenylcyclopenta[*b*]indol-3-one **333** or 3-phenylcyclopenta[*b*]indol-1-one **334**. To establish the regiochemistry of the second component a proton NOESY NMR experiment was attempted. Unfortunately the sample decomposed in solution and no definitive assignment of the regiochemistry has been possible.

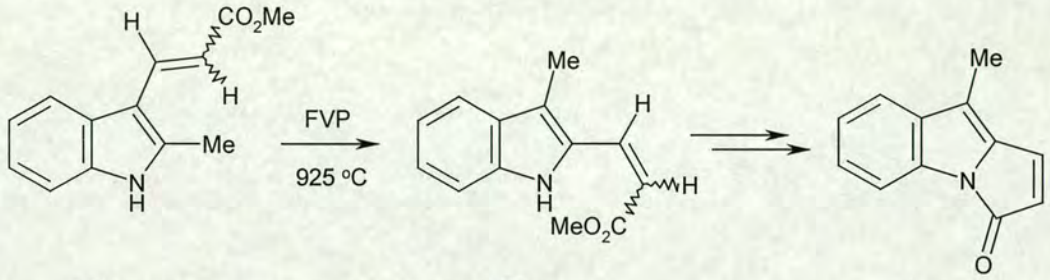
The formation of 1-phenylcyclopenta[*b*]indol-3-one **333** may result from sequential [1,5] hydrogen shifts of **302** followed by elimination of methanol to generate the ketene intermediate **335**. Electrocyclisation at the indole C-2 and a subsequent [1,5] hydrogen shifts to restore the aromaticity affords **333**. In a similar fashion 3-phenylcyclopenta[*b*]indol-1-one **334** may result from sequential [1,5] hydrogen shifts and a [1,5] propenoate shift followed by elimination of methanol to generate the ketene intermediate **336**. Electrocyclisation at the indole C-3 and subsequent [1,5] hydrogen shifts affords **334** (Scheme 102).



Scheme 102

The pyrolysis of 3-(2-methylindol-3-yl)-acrylic acid methyl ester **312** proved ineffective in the synthesis of 9-methylpyrrolo[1,2-*a*]indol-3-one **78**. A range of furnace temperatures were used with the optimum conversion of the precursor being

925 °C. A solid yellow/brown pyrolysate was obtained that was analysed by proton NMR spectroscopy and characteristic signals of 9-methylpyrrolo[1,2-*a*]indol-3-one **78**, an enone doublet at 5.81 ppm and a methyl singlet at 2.19 ppm, were present in the spectrum but in only small quantities.[19] The majority of the pyrolysate was found to be decomposition products (Scheme 103).



312 **337** **78**

Scheme 103

The presence of some 9-methylpyrrolo[1,2-*a*]indol-3-one **78** indicates that the migration of the propenoate from the indole 3-position to the indole 2-position and the subsequent methyl migration in the opposite direction does occur to afford the indole 2-propenoate **337**, but at a much slower rate than that of the propenoate/proton migration in the formation of **2** and its derivatives **326** and **328** and as such decomposition pathways have a much greater effect during the pyrolysis.

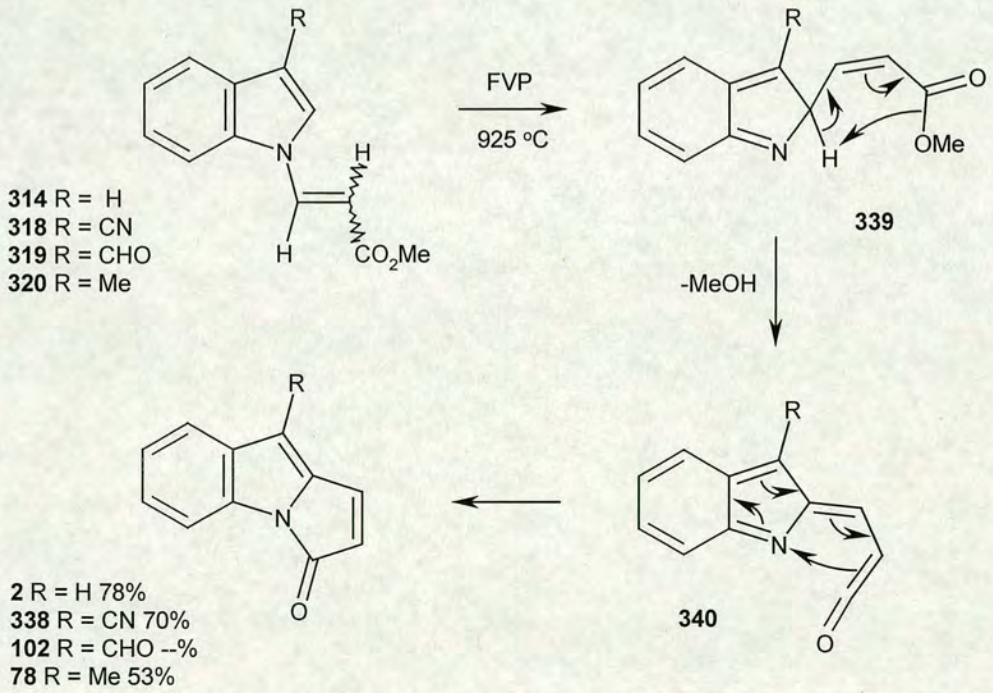
2.3.4.2 Flash vacuum pyrolysis of indole *N*-propenoate precursors

The gas phase pyrolyses of the indole *N*-propenoate precursors **314**, **318-320** were performed at a temperature 925 °C. Small-scale pyrolyses at 900 °C, 925 °C and 950 °C had demonstrated that this was the optimum temperature for full conversion of the precursors to products. The inlet temperatures required for volatilisation ranged between 160-210 °C and were carefully set to obtain the optimum sublimation to minimise any degradation of the precursor.

The parent benzopyrrolizinone precursor was trapped using a U-tube trap but in all other pyrolyses a dry ice/acetone cold-finger trap was used. In all cases the

yellow/orange pyrolysate obtained was removed from the trap for immediate analysis by ^{1}H NMR spectroscopy leaving small quantities of insoluble white polymeric material in the trap. Where single products were obtained, purification by dry flash chromatography was performed (generally with a DCM and/or ethyl acetate in hexane solvent system as eluent) to obtain the pure benzopyrrolizin-3-one product.

A preparative pyrolysis of **314** (300 mg) afforded pyrrolo[1,2-*a*]indol-3-one **2** as a yellow solid. The pyrolysis proceeded smoothly with a constant rate of volatilisation and reached completion after 40 min. Removal of the crude product and purification gave a 78% yield of **2**. Pyrolysis of the cyano precursor **318** gave an orange pyrolysate although some material condensed on the furnace exit/trap inlet and underwent thermal degradation. The majority of the product collected on the cold-finger surface and upon completion of the pyrolysis was washed from the finger in acetone and purified by dry flash chromatography to afford a 70% yield of 9-cyanopyrrolo[1,2-*a*]indol-3-one **338** (Scheme 104).



Scheme 104

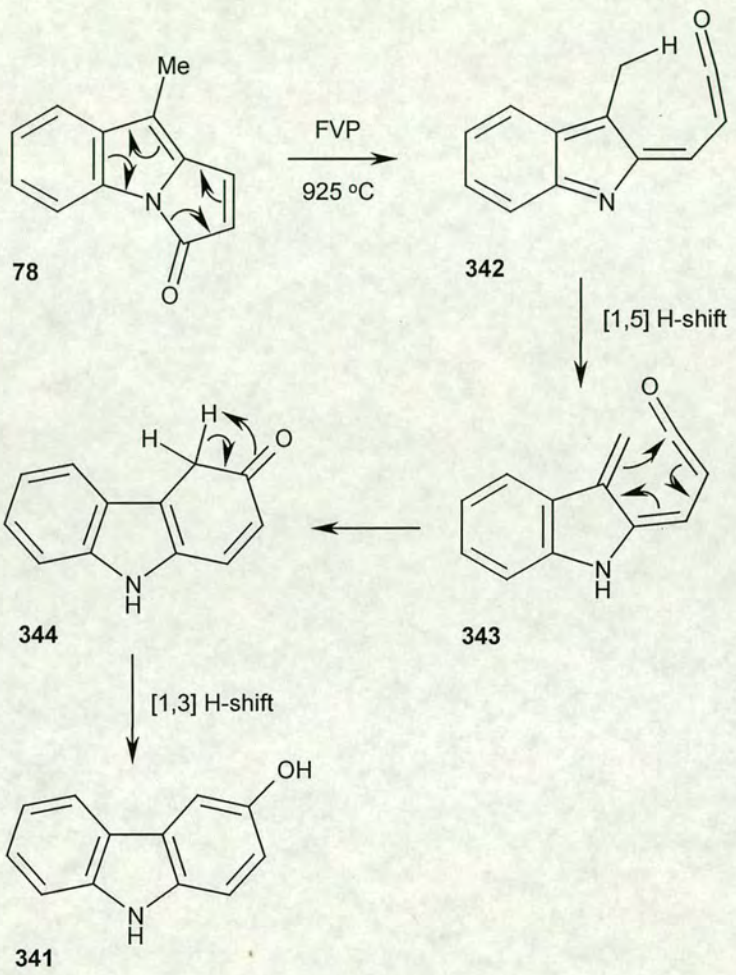
The mechanism of formation of the benzopyrrolizin-3-one products is the same as that in the syntheses of pyrrolizin-3-ones and azabenzopyrrolizin-1-ones. The rate determining nitrogen-to-carbon migration of the propenoate generates the 2*H*-indole propenoate **339** that undergoes loss of methanol to give the ketene **340** followed by electrocyclisation to form the lactam products.

The pyrolyses of the formyl precursor **319** and the methyl precursor **320** were complicated by side reactions during pyrolysis. Whilst a 53% yield of 9-methylpyrrolo[1,2-*a*]indol-3-one **78** was obtained, the pyrolysis of **319** afforded no 9-formylpyrrolo[1,2-*a*]indol-3-one **102** at all.

In the formation of 9-methylpyrrolo[1,2-*a*]indol-3-one **78** a substantially lower yield than for **2** and **338** was achieved. T. L. C. and proton NMR spectroscopy indicated that the crude pyrolysate contained a large quantity of side product occurring in a 1:1 ratio with **78**. A dry flash column was run to isolate the two major products which were identified in order of elution as 9-methylpyrrolo[1,2-*a*]indol-3-one **78** and 9*H*-carbazol-3-ol **341** (identified by comparison of the NMR spectra and mass spectrum with reported data),[85] obtained in 53% and 47% yields respectively. To establish whether the carbazol-3-ol **341** side product was formed directly from the precursor **320** or by rearrangement of the benzopyrrolizinone **78** a pyrolysis of **78** was performed under the same conditions as those used for pyrolysis of the precursor **320**. The proton NMR spectrum of the crude pyrolysate indicated, by comparison with authentic data, that a 1:1 mixture of 9-methylpyrrolo[1,2-*a*]indol-3-one **78** and 9*H*-carbazol-3-ol **341** was formed. This result strongly suggests that the carbazol-3-ol **341** is formed by a rearrangement of the benzopyrrolizinone **78** rather than by a competing mechanistic route from the precursor **320**.

A possible mechanism for the formation of carbazol-3-ol **341** from 9-methylpyrrolo[1,2-*a*]indol-3-one **78** upon pyrolysis involves ring-opening of the lactam bond to form the ketene intermediate **342** after which a [1,5] hydrogen shift restores the aromaticity of the benzene ring to give **343**. Electrocyclisation of the

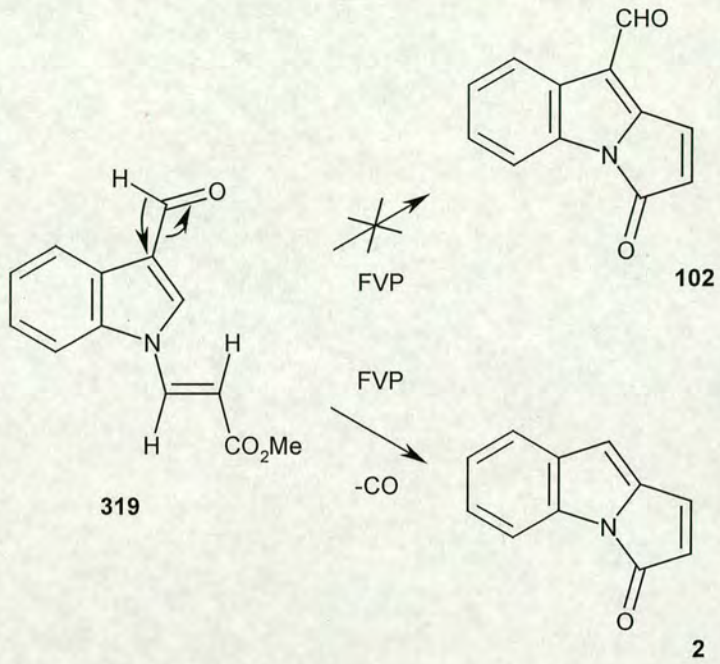
indole methylene at the ketene carbonyl carbon to give **344** is followed by enol formation to generate the fully aromatic 9*H*-carbazol-3-ol **341** (Scheme 105).



Scheme 105

Pyrolysis of the 3-formyl precursor **319** was performed at 925 °C with a dry ice/acetone cold-finger trap. A yellow pyrolysate collected on the cold-finger surface and upon completion of the reaction was washed from the trap with acetone under a nitrogen atmosphere. After removal of the acetone the pyrolysate was analysed by proton NMR spectroscopy which showed that the product was solely pyrrolo[1,2-*a*]indol-3-one **2**, obtained in 94% yield, and not 9-formylpyrrolo[1,2-*a*]indol-3-one **102** (Scheme 106). The product **2** is generated by thermal decarbonylation which has

previously been reported, although in this case it has not been established at which point during the pyrolysis decarbonylation occurs.[86]

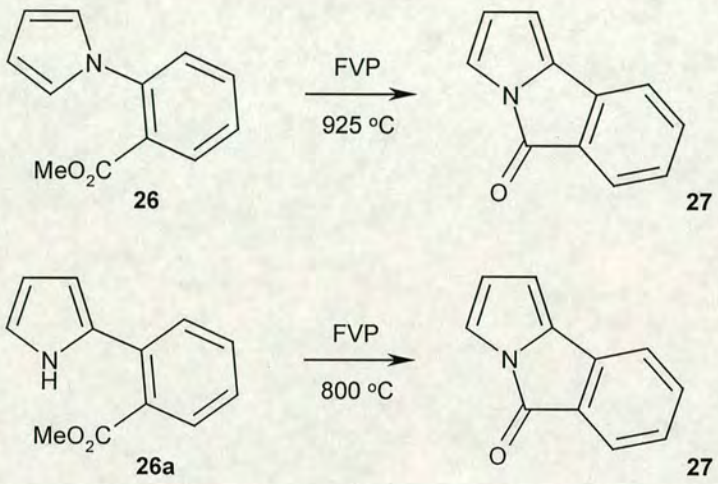


Scheme 106

2.3.4.3 Flash vacuum pyrolysis of indole *N*-benzoate precursors

The indole *N*-benzoate precursors **323** and **325** were pyrolysed over a range of temperatures using the apparatus shown in section 3.2.9 (Figure 14). Small scale pyrolyses (30 mg) over 10 min with inlet temperatures of 100-120 °C gave solid yellow pyrolysates. It was found that a higher furnace temperature of 950 °C, with silica tubes placed near the furnace exit, was needed for full conversion of the precursors to products. The silica tubes cause an increase in furnace residence time and so have the effect of raising the furnace temperature by *ca.* 50 °C. The furnace temperatures used are even higher than those used in benzopyrrolizin-3-one synthesis and reflect an increased energy requirement. As previously stated, there is an increased energy requirement for the pyrolysis of the benzimidazole *N*-propenoate **290** relative to the imidazole *N*-propenoate **254** due to the need to form an *o*-quinonoid system upon migration of the propenoate group in **290**. However, there is also some evidence to suggest that benzoate migration is slower than propenoate

migration and therefore also requires a higher furnace temperature. The pyrrole *N*-benzoate **26** requires a temperature of 925 °C for full conversion to the lactam **27** (section 1.1.1.2, Scheme 3) which is 50-100 °C greater than the imidazole *N*-propenoates. It is likely that the increased energy requirement is not for breaking the aromaticity of the benzene ring since pyrolysis of the analogous pyrrole 2-benzoate **26a** can be performed at 800 °C.[45]



Scheme 107

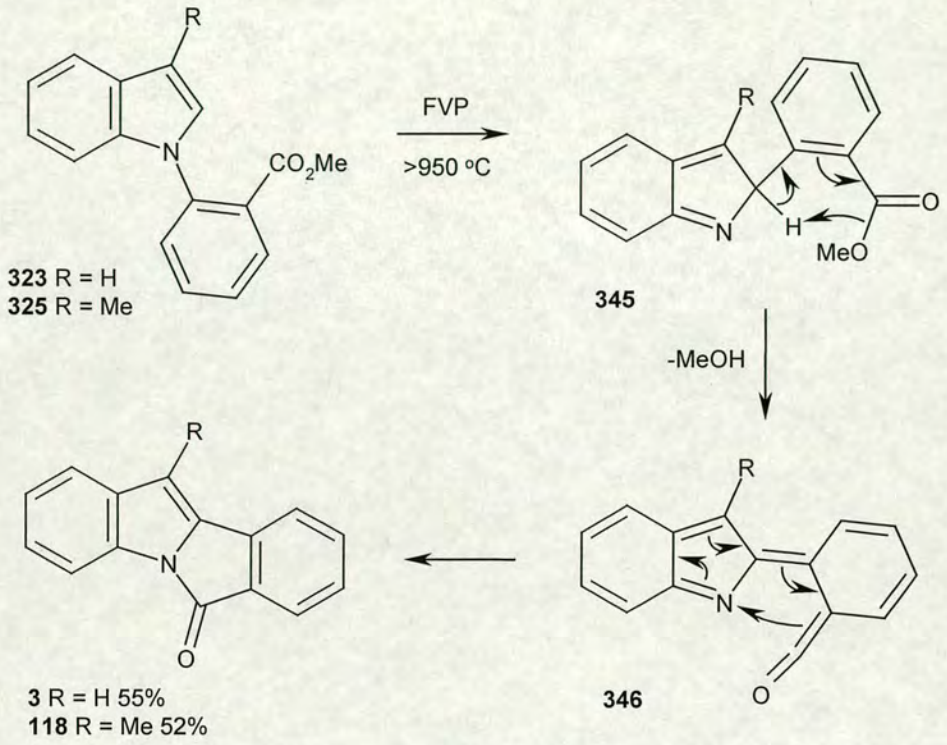
It therefore seems likely that the higher temperature needed for pyrolysis of the indole *N*-benzoates **323** and **325** is required, not for the formation of the intermediate **346**, but for the formation of the *o*-quinonoid system upon the slower migration of the benzoate substituent. If the higher temperature was for the formation of **346** then pyrolyses performed at temperatures slightly below the optimum temperature may be expected to contain some indole 2-benzoate resulting from migration of the benzoate to form **345** followed by a [1,5] hydrogen shift from C-2 to the indole nitrogen. However, such a product is not observed in any of the proton NMR spectra (authentic sample gives pyrrole resonance at δ_H 6.64 ppm and ester methyl at δ_H 3.78 ppm from ring-opening of **3** with methoxide, section 2.4.3.2) of pyrolyses performed at 925 °C and 950 °C.

A preparative pyrolysis (400 mg) of **323** using the U-tube trap was performed and it was apparent that thermal degradation of the product was occurring due to the pyrolysate condensing very close to the furnace exit. Complete volatilisation of the precursor required 40 min after which the trap was warmed to room temperature under a nitrogen atmosphere. The pyrolysate was dissolved into chloroform and purified by dry flash chromatography to afford the dibenzopyrrolizinone, isoindolo[2,1-*a*]indol-6-one **3**, in 76% yield. A preparative pyrolysis (265 mg) of the methyl substituted precursor **325** was also performed but utilised a dry ice/acetone cold-finger trap rather than the standard U-tube trap in an effort to keep the pyrolysate cold and hence reduce the thermal degradation. Unfortunately, despite attempts to keep the furnace exit/trap inlet warm by wrapping it in foil, the pyrolysate again condensed at the furnace exit with little product being trapped on the cold-finger surface. After collection and purification by dry flash chromatography a 72% yield of 11-methylisoindolo[2,1-*a*]indol-6-one **118** was nevertheless obtained.

The yields of 72-76% are similar to those obtained in other pyrolyses and the thermal degradation at the trap caused by the extreme temperatures required for formation of the products is the prime cause of the loss of product in this process. The yields may be improved by the combined effect of better lagging of the furnace exit/trap inlet and reduction of the distance between the furnace exit and the cold-finger surface. The use of a diffusion pump may also be beneficial by virtue of the lower pressure allowing products to travel further before condensation.

The high furnace temperatures are required for the migration of the benzoate group to the indole 2-position. This is demonstrated by the recovery of increasing quantities the precursors **323** and **325** in the pyrolysates when furnace temperatures are reduced sequentially. The mechanism of formation is very similar to that of benzopyrrolizinone formation from indole *N*-propenoate precursors and involves an initial nitrogen-to-carbon migration of the benzoate to generate **345** followed by the elimination of methanol that requires breaking of the aromaticity of both benzene rings to afford the ketene intermediate **346**. However, the high temperature needed to

initiate migration is more than sufficient to break aromaticity. Restoration of aromaticity drives the electrocyclisation to the tetracyclic isoindolo[2,1-*a*]indol-6-one products **3** and **118** (Scheme 108).



Scheme 108

2.3.5 Scope of benzo[1,2-*a*]pyrrolizin-3-one synthesis by rearrangement flash vacuum pyrolysis process

The rearrangement FVP technique has provided a general method *via* two complementary routes for the synthesis of 1-, 2- and 9-substituted benzopyrrolizin-3-ones. The method is general and in most cases the products are obtained in two steps from available staring materials in overall yields of 46-75% with the potential for more derivatives to be synthesised in the same manner.

The technique has allowed direct access to a 2-monosubstituted benzopyrrolizin-3-one for the first time. The previous method of synthesis (section 1.1.2.3.3), by pyrolysis of Meldrum's acid derivatives, is dependent upon a rearrangement of the

methyleneketene intermediate **80** *via* a [1,7] hydrogen shift to the eventual benzopyrrolizin-3-one 2-position and therefore such a substitution pattern was inaccessible.

The benzopyrrolizin-3-one FVP products are usually the only product from pyrolysis with the major cause of reduced yields being thermal degradation of the product at the furnace exit/trap inlet despite the use of cold-finger traps. It may be advantageous for future pyrolyses to utilise a diffusion pump. The increased vacuum in the system is likely to have two beneficial effects on the pyrolyses. The lowering of the required inlet temperature may reduce any degradation of the precursor in the inlet and at the trap a greater degree of condensation of the product onto the cold-finger surface may be attained and in doing so higher yields of benzopyrrolizin-3-one products should be achieved.

The increased stability of benzopyrrolizinones relative to azapyrrolizinones and azabenzopyrrolizinones affords simple purification by dry flash chromatography. Highly polar eluent systems (generally ethyl acetate and/or DCM in hexane) are used to obtain pure compounds in short periods since the benzopyrrolizin-3-one products are eluted in the initial fractions whereas the degradation products are generally more polar.

Some synthetic problems are apparent. Not all substituents are suitable for pyrolysis, for example the dimethyl ester precursor **300** fails to give any product and the 3-formyl precursor **319** undergoes decarbonylation to afford the parent system **2**. The 9-methylpyrrolo[1,2-*a*]indol-3-one precursor **320** and to a lesser extent the 1-phenylpyrrolo[1,2-*a*]indol-3-one precursor **302** are susceptible to a side reaction during pyrolysis. Whilst the problem is insignificant in the formation of 1-phenylpyrrolo[1,2-*a*]indol-3-one **328**, the formation of 9-methylpyrrolo[1,2-*a*]indol-3-one **78** is arguably still best achieved by the pyrolysis of the Meldrum's acid derivative (section 1.1.2.3.3), although access to the precursor is difficult and not high yielding. In this case the pyrolysis is performed at 600 °C rather than 925 °C as in the rearrangement FVP route and as such the temperature is sufficiently high to

generate 9-methylpyrrolo[1,2-*a*]indol-3-one **78** but low enough not to cause ring-opening and formation of 9*H*-carbazol-3-ol **341**.

2.3.6 Spectroscopic properties of benzo[1,2-*a*]pyrrolizin-3-ones

The benzopyrrolizinone products were all characterised by ^{1}H NMR, ^{13}C NMR and mass spectroscopy and by comparison with literature data where possible.[19] Where new compounds have been obtained accurate mass analysis has also been obtained. No HSQC experiments were performed and hence carbon resonances are not assigned. Infra-red and UV/visible data are also recorded.

2.3.6.1 ^{1}H NMR spectra

The chemical shifts of the benzopyrrolizin-3-one H-1, H-2 and H-9 proton resonances are shown in Table 17 and have been assigned by comparison with pyrrolizin-3-one **1**.[56] The H-1 and H-2 proton resonances of pyrrolo[1,2-*a*]indol-3-one **2**, at δ_H 7.02 ppm and δ_H 5.86 ppm respectively, are similar to those of pyrrolizin-3-one **1** (at δ_H 7.04 ppm and δ_H 5.63 ppm respectively) whereas the H-9 resonance of **2** is more akin to that of indole (δ_H 6.50 ppm) than the corresponding signal of pyrrolizin-3-one **1** (δ_H 5.95).[60]

Compound	Substituent	δ_H/ ppm ($CDCl_3$)			
		H-1 (Hz)	H-2 (Hz)	H-9	Aromatics
2	---	7.02 (*J* 5.8)	5.86 (*J* 5.8)	6.27	7.58-6.96
328	1-phenyl	---	6.08	6.64	7.68-7.03
326	2-cyano	7.70	---	6.79	7.71-7.16
338	9-cyano	7.30 (*J* 6.0)	6.14 (*J* 6.0)	---	7.66-7.18
78	9-methyl	7.08 (*J* 5.9)	5.81 (*J* 5.9)	---	7.58-7.02
3	---	---	---	6.52	7.76-7.03

Table 17 – Chemical shifts and coupling constants of benzopyrrolizin-3-ones

The presence of a cyano group has the effect of shifting the remaining 5-membered ring resonances to higher frequency by virtue of its strong electron withdrawing properties. In 2-cyanopyrrolo[1,2-*a*]indol-3-one **326** the H-1 resonances is shifted by ~0.7 ppm and the H-9 by ~0.5 ppm relative to the parent **2**. A similar but smaller effect occurs for 9-cyanopyrrolo[1,2-*a*]indol-3-one **338** in which the H-1 and H-2 resonances are both shifted by ~0.3 ppm. The anisotropic effects of the phenyl substituent in 1-phenylpyrrolo[1,2-*a*]indol-3-one **328** causes the H-2 and H-9 resonances to move to higher chemical shift by 0.22 ppm and 0.37 ppm respectively relative to **2** whereas the chemical shifts of H-1 and H-2 of 9-methylpyrrolo[1,2-*a*]indol-3-one **78** are very similar to those of **2**. Isoindolo[2,1-*a*]indol-6-one **3** has only one characteristic resonance, the 'pyrrole' proton, that is at 6.52 ppm and is in accordance with other pyrrole type resonances of benzopyrrolizin-3-ones.

In all cases where H-1 and H-2 protons are present the coupling constants are very similar in value, between 5.8-6.0 Hz, and show no difference to those obtained in pyrrolizin-3-ones but are much smaller than those in the benzene ring and therefore easily identified.[87]

2.3.6.2 Mass spectra, UV/visible and infra-red spectra

The mass spectra of benzopyrrolizin-3-ones all show strong molecular ion (M^+) peaks which, with the exception of 9-cyanopyrrolo[1,2-*a*]indol-3-one **338**, are also the base peaks. The initial fragmentation is the loss of CO (M^+ -28), however, subsequent fragmentation may follow competing pathways as the spectra are complex with no clear fragmentation peaks identifiable in the spectra as a whole.

The UV/visible spectra were recorded in chloroform and show absorption bands at 358-386 nm. These bands give rise to the intense colouration of the benzopyrrolizinone products and are thought to be associated with an electronic transition in the pyrrolone ring.[48] The absorption bands recorded are similar to literature data for known benzopyrrolizinones but appear to show no pattern according to the substituent present except that all show a bathochromic shift.[19]

Compound	Substituent	λ_{max}/nm
2	---	358
328	1-phenyl	372
326	2-cyano	386
338	9-cyano	373
78	9-methyl	374
3	---	361
118	11-methyl	365

Table 18 – Absorption bands of (di)benzopyrrolizin-3-ones

The infra-red spectra of the benzopyrrolizin-3-ones (Table 19) show remarkably high positions of the carbonyl stretching frequency.

Compound	Substituent	ν_{max}/cm^{-1}
2	---	1720
328	1-phenyl	1715, 1609
326	2-cyano	1727
338	9-cyano	1735
78	9-methyl	1715
3	---	1729, 1611
118	11-methyl	1709, 1609

Table 19 – Carbonyl stretching frequencies of (di)benzopyrrolizin-3-ones

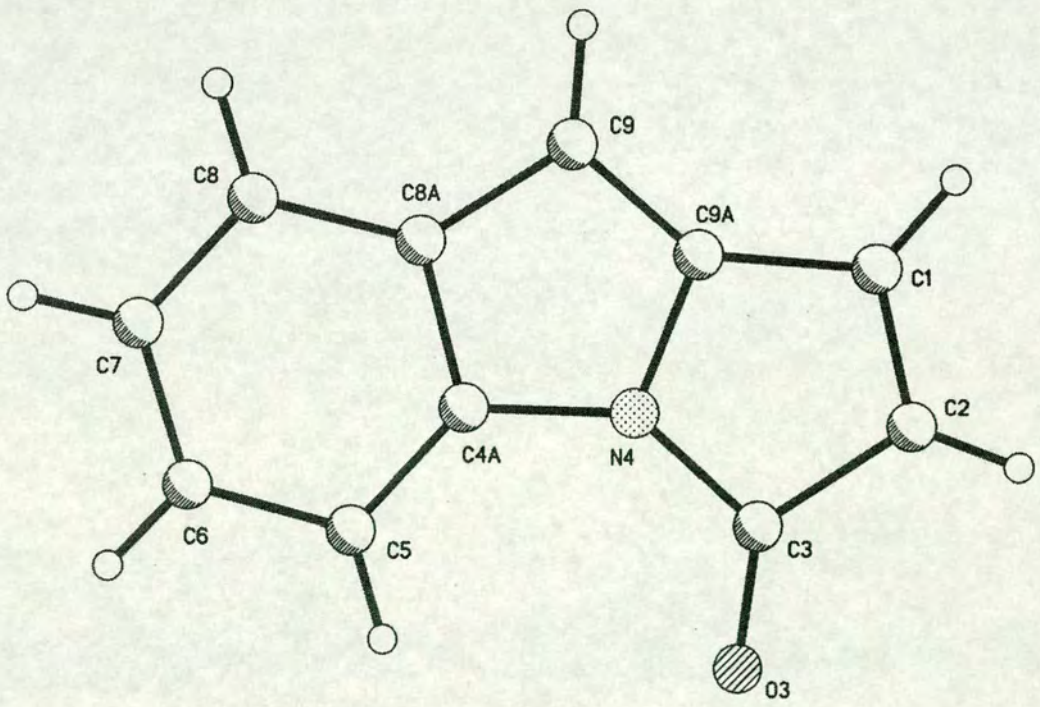
The carbonyl signals are found between 1709-1748 cm^{-1} and considerably higher than would be expected of a typical amide. However, the position of the stretches are

consistent with those previously observed for pyrrolizinones and pyrroloimidazolones and are a result of a lack of the usual amide type delocalisation.[88,11] A band found at ~1610-1630 cm^{-1} is present in the isoindolo[2,1-*a*]indol-6-ones **3** and **118** but similar bands are not observed for the pyrrolo[1,2-*a*]indol-3-ones, with the exception of 1-phenylpyrrolo[1,2-*a*]indol-3-one **328**, and may be associated with the stretching frequencies of the 1,2 annulated benzene ring.

2.3.6.3 Solid state structure

Crystallisation of pyrrolo[1,2-*a*]indol-3-one **2** and isoindolo[2,1-*a*]indol-6-one **3** by slow evaporation of solvent gave samples suitable for X-ray analysis.

Two sets of bond length and bond angles were obtained for **2** due to the presence of two independent molecules in the unit cell but the data are not significantly different. The two structures are shown in Figure 4 and bond length and bond angle data presented in Table A (Appendix).



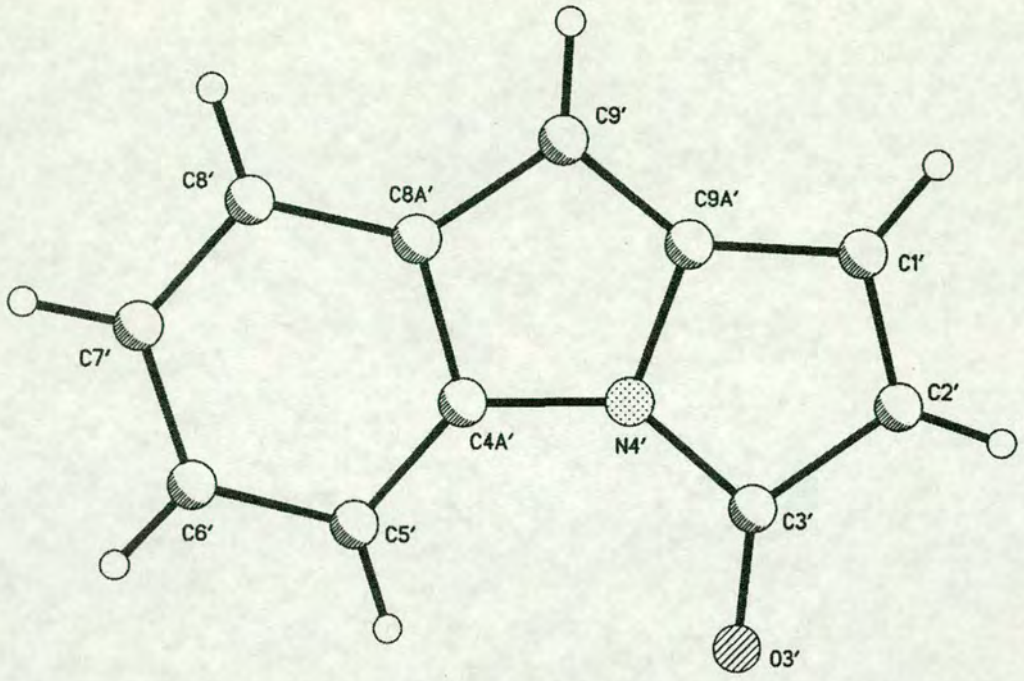


Figure 4 – crystal structure of pyrrolo[1,2-*a*]indol-3-one **2**

The structure of pyrrolo[1,2-*a*]indol-3-one **2** shows one significant difference to that of the non-annulated analogue pyrrolizin-3-one **1** in terms of bond lengths.[88] The length of the benzene/pyrrole fused bond which in **2** is 1.4095(18) Å [or 1.4102(19) Å in the second molecule] is much longer than the equivalent bond in **1** which is 1.3523(17) Å. The bond length is more akin to that of the fused bond observed in pyrrolo[2,1-*a*]isoindol-5-one **27** (1.402(2) Å) and in both cases the fused bond is also the longest bond in the benzene ring.[11] The other pyrrole and pyrrolone ring bond lengths are all similar to those of pyrrolizin-3-one **1**.

Comparison of the C-N [1.3937(18) Å and 1.3945(17) Å] and C=O (1.2092(19) Å and 1.2080(18) Å) bond lengths with typical values for amides [*i.e.* γ-lactams C-N 1.344(14) Å and C=O 1.205(6) Å][89] suggest that there is no normal amide type delocalisation of the nitrogen lone-pair into the carbonyl group. The delocalisation of the nitrogen lone-pair into the ring system is also supported by the planarity of the molecule in which large exocyclic bond angles [for example bond angle C(9)-C(9A)-C(1) is 143.89 °] are a consequence of the molecule adopting a planar geometry to

attain the maximum π-orbital overlap possible. Such planarity and bond angles have also been observed in pyrrolizin-3-one **1** and pyrrolo[2,1-*a*]isoindolo-5-one **27** and in this respect pyrrolo[1,2-*a*]indol-3-one **2** is very similar.[88,11]

The data obtained for isoindolo[2,1-*a*]indol-6-one **3**, shown in Figure 5, (Appendix, Table B) is not of great accuracy due to disorder in the crystal packing but simple comparisons with **2** can be drawn. The same lengthening of the fused bond relative to the non-annulated species **1** is observed as well as the amide linkage having comparable bond lengths to those of **1**, **2** and **27**. The planar geometry and large bond angles are also present and suggest that isoindolo[2,1-*a*]indol-6-one **3** has little normal amide delocalisation too.

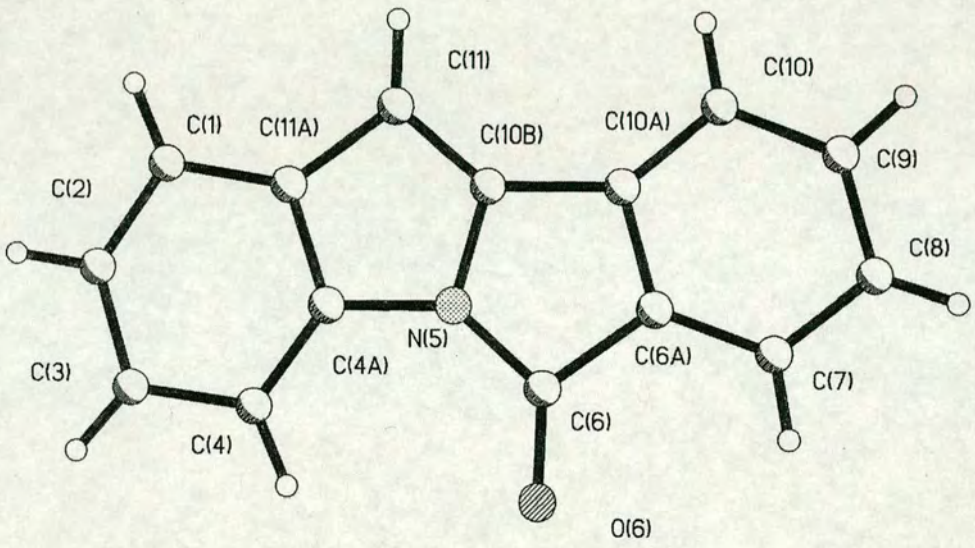


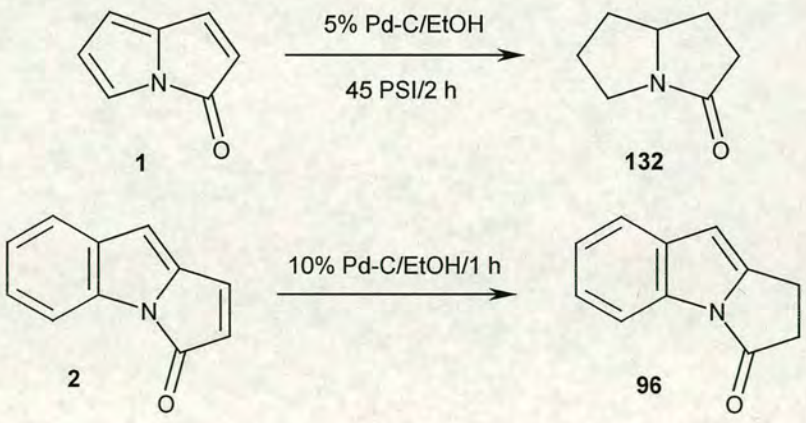
Figure 5 - crystal structure of isoindolo[2,1-*a*]indol-6-one **3**

2.4 Chemistry of benzopyrrolizinones and azabenzopyrrolizinones

Whilst the chemistry of pyrrolizinone has been examined, little chemistry of the benzopyrrolizinones and azabenzopyrrolizinones has been reported. This chapter describes investigations into the chemical reactivity of these systems and is concerned with hydrogenation, cycloaddition and reactivity towards nucleophiles.

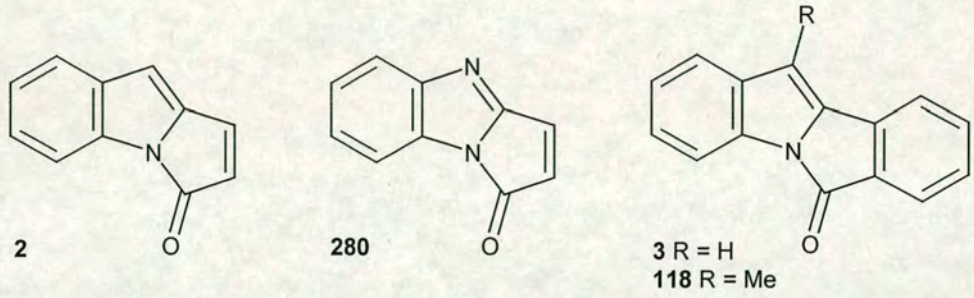
2.4.1 Hydrogenation reactions

Extensive study into the catalytic hydrogenation of the pyrrolizin-3-one system, using a range of catalysts and solvents, has shown that the optimum catalytic system for hydrogenation of the parent compound **1** is Pd/C in ethanol. Hydrogenation of the 1,2-bond of **1** occurs readily under mild conditions and complete hydrogenation to the pyrrolizidin-3-one **132** can be achieved using a catalytic quantity of 5% Pd/C in ethanol over 2 h under 45 PSI of hydrogen at room temperature. In the hydrogenation of 1- and 7-monosubstituted pyrrolizin-3-one, the highest degree of diastereomeric selectivity is obtained using palladium or rhodium catalysts.[44] Hydrogenation of pyrrole occurs at pressures in excess of 1000 PSI and although the presence of an electron withdrawing group does facilitate more ready hydrogenation the conditions for hydrogenation of **1** are unusually mild.[90] The 1,2-bond of pyrrolo[1,2-*a*]indol-3-one **2** has also been shown to be readily hydrogenated under a hydrogen atmosphere with 10% Pd/C catalyst over 1 h in ethanol but no complete hydrogenation has been reported (Scheme 109).[31,43]



Scheme 109

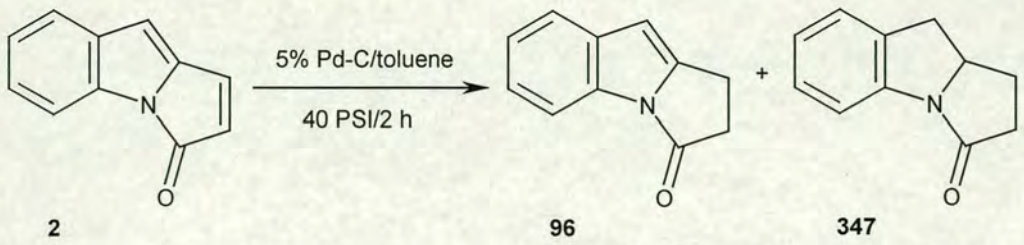
A series of hydrogenation reactions were performed at both medium (40-60 PSI) and high (300-1100 PSI) pressures using pyrrolo[1,2-*a*]indol-3-one **2**, pyrrolo[1,2-*a*]benzimidazol-1-one **280**, isoindolo[2,1-*a*]indol-6-one **3** and its 11-methyl derivative **118**.



2.4.1.1 Medium pressure hydrogenations

All hydrogenations were performed using the same general method. The substrate (30-50 mg) was dissolved in solvent (15-12 cm^3) and hydrogenated with a heterogeneous catalyst (~5 mg) over a recorded time interval. The catalyst was removed by filtration through a celite pad followed by evaporation of the solvent *in vacuo* to give the crude hydrogenation products.

Hydrogenation of pyrrolo[1,2-*a*]indol-3-one **2** with 5% Pd-C at 40 PSI over 2 h in toluene was found to give a 97% yield of material consisting largely 1,2-dihydropyrrolo[1,2-*a*]indol-3-one **96** which was obtained as a colourless solid. The ^1H NMR spectrum indicated that the hydrogenation product also contained 1,2,9,9a-tetrahydropyrrolo[1,2-*a*]indol-3-one **347**, as ~8% of the product, that was tentatively identified by characteristic signals due to saturated functions at δ_H 4.57-4.51 ppm and 2.86-1.83 (Scheme 110).



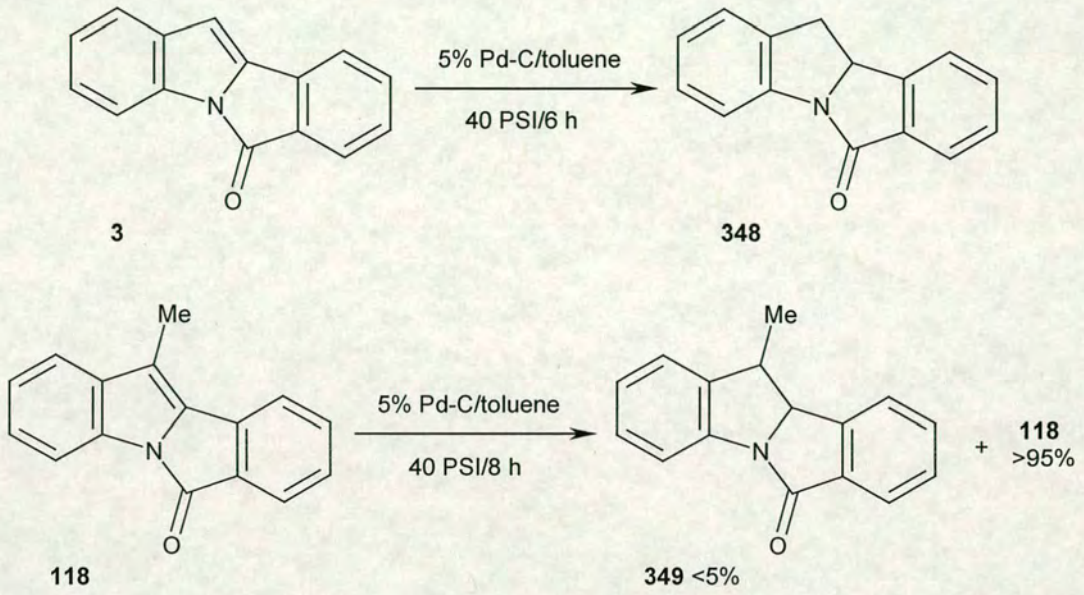
2 96 347

Scheme 110

Two further hydrogenations at 60 PSI with 5% Pd-C and 5% Rh-C failed to increase the proportion of the tetrahydro species **347** in the hydrogenation products. That the 9-9a bond is not hydrogenated under these conditions is, perhaps, in accordance with the hydrogenation conditions required for indoles and pyrroles, however, there is no clear reason why the 9-9a bond should not be hydrogenated under similar conditions to that of pyrrolizinone **1** since both contain the electron withdrawing enone moiety.

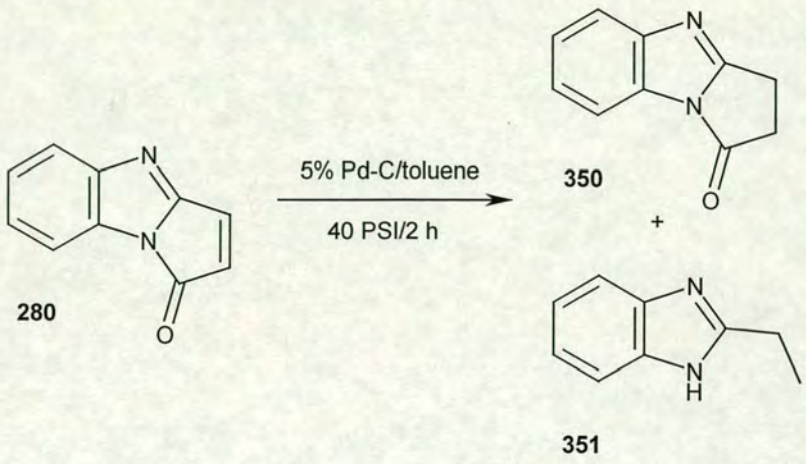
Isoindolo[2,1-*a*]indol-6-one **3** afforded 10b,11-dihydroisoindolo[2,1-*a*]indol-6-one **348** when hydrogenated with 5% Pd-C at 40 PSI over 6 h in toluene as a colourless solid in quantitative yield. The product was identified from the proton NMR spectrum by a triplet at δ_H 5.52 ppm and two double doublets at δ_H 3.37 ppm and δ_H 2.95 ppm due to the 10b ring junction proton and the two methene protons at C-11 respectively. The reduced aromaticity of the 10b,11 bond relative to the equivalent bond in pyrrolo[1,2-*a*]indol-3-one **2**, may result from the increased electron withdrawing character of the fused benzene ring relative to the 1,2-double bond in **2** therefore allowing complete hydrogenation across the bond rather than the small degree of hydrogenation obtained for **2**. However, hydrogenation of 11-methyl-isoindolo[2,1-*a*]indol-6-one **118** under the same conditions over 8 h gave no hydrogenation product. A second hydrogenation of **118** at 60 PSI with 5% Rh-C over 8 h returned largely starting material with a trace (<5%) of 10b,11-bond hydrogenation product, 10b,11-dihydro-11-methylisoindolo[2,1-*a*]indol-6-one **349**, identified by its proton NMR spectrum showing a 10b ring junction proton doublet at δ_H 5.53 ppm, a quintet at δ_H 3.62 ppm of the C-11 proton and a methyl doublet at δ_H

0.76 ppm. The resistance to hydrogenation is presumably due to the steric bulk of the methyl group hindering access to the catalyst surface (Scheme 111).



Scheme 111

Pyrrolo[1,2-*a*]benzimidazol-1-one **280** is much less stable than pyrrolo[1,2-*a*]indol-3-one **2** and is perhaps not surprisingly more reactive towards hydrogenation. The proton NMR spectrum of the reaction products from the hydrogenation of **280** in toluene with 5% Pd-C at 40 PSI for 2 h, the same conditions as used for hydrogenation of **2**, indicated the presence of two hydrogenation products a in 50:50 mixture. These products were identified as 2,3-dihydropyrrolo[1,2-*a*]benzimidazol-1-one **350** and 2-ethylbenzimidazole **351** by comparison with literature data (Scheme 112).[91,92]



Scheme 112

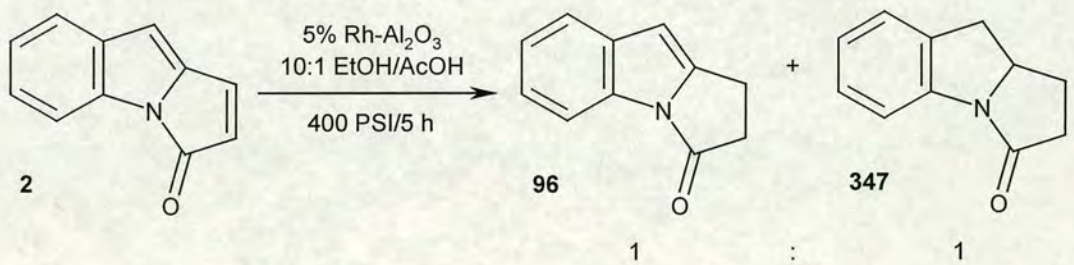
A second hydrogenation was performed under identical conditions but over just 30 min to determine whether 2-ethylbenzimidazole **351** was being formed from the 2,3-dihydro compound **350**. A ^{1}H NMR spectrum of the resultant material showed both 2,3-dihydropyrrolo[1,2-*a*]benzimidazol-1-one **350** and 2-ethylbenzimidazole **351** were present and that a trace of pyrrolo[1,2-*a*]benzimidazol-1-one **280** still remained. This strongly suggests that selective reduction of the 2,3 double bond is not possible under these conditions with Pd/C catalysts.

The formation of the 2,3-dihydropyrrolo[1,2-*a*]benzimidazol-1-one **350** was expected but the formation of 2-ethylbenzimidazole **351** through reduction by hydrogenation is unprecedented in pyrrolizinone chemistry. Indeed, in a review of benzimidazole reduction no such reduction process is reported.[93] No mechanism for the reductive decarbonylation under hydrogenation conditions has been rationalised.

2.4.1.2 High pressure hydrogenations

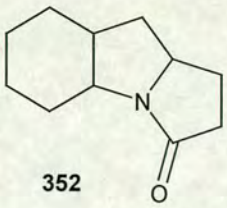
High pressure hydrogenations were performed in a similar manner to those at medium pressure: the substrate was dissolved in solvent and heterogeneous catalyst added then transferred to the reaction vessel and hydrogenated over a recorded time interval. The work-up was by filtration through a celite pad, and evaporation of the solvent gave the crude hydrogenation products.

In an attempt to force hydrogenation of the 9,9a-bond, several hydrogenations of pyrrolo[1,2-*a*]indol-3-one **2** were performed at 600 PSI at temperatures between 20-60 °C with 5% Pd-C or 5% Rh-C catalysts. However, the largest degree of hydrogenation reached under these conditions was an apparent 90:10 equilibrium mixture of the dihydro **96** and tetrahydro **347** derivatives respectively which is no greater than that obtained at a pressure of 40 PSI. Having had little success in hydrogenating the 9-9a-bond of **2**, a literature search showed that Gilchrist and Graham had found that the reduction of *N*-*t*-butoxycarbonylindoles was best carried out at 200 PSI over a rhodium-alumina catalyst in a 10:1 mixture of ethanol and acetic acid to afford the corresponding 2,3-dihydroindoles in good yields.[95] In changing the catalytic system a hydrogenation of **2** over 5 h at room temperature and 400 PSI using 5% Rh-Al_2O_3 in a 10:1 mixture of ethanol and acetic acid gave a 1:1 mixture of the dihydro **96** and tetrahydro **347** derivatives as shown by proton NMR spectroscopy. Also present in the proton NMR spectrum were signals suggesting that a small degree of hydrogenation of the benzene ring had occurred. Dry flash chromatography allowed separation of the two major components of the reaction mixture to give 1,2-dihydropyrrolo[1,2-*a*]indol-3-one **96** in 46% yield and 1,2,9,9a-tetrahydropyrrolo[1,2-*a*]indol-3-one **347** in 42% yield (Scheme 113).



Scheme 113

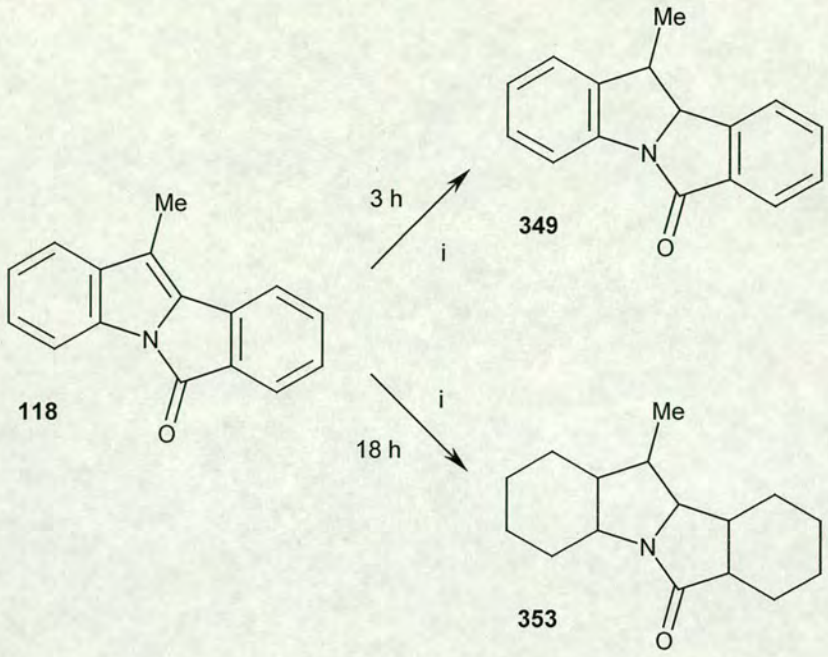
A second hydrogenation under the same conditions but over 8 h gave complete consumption of the dihydro derivative **96** with products ranging from the tetrahydro derivative **347** to the fully hydrogenated decahydropyrrolo[1,2-*a*]indol-3-one **352**.



352

The presence of the fully saturated system **352** indicates that quantitative selective reduction to the tetrahydro derivative **347** is not possible using these conditions, however, lowering the hydrogenation pressure may be beneficial in attaining more selectivity in reduction.

High pressure hydrogenation of 11-methylisoindolo[2,1-*a*]indol-6-one **118** was also performed due to its resistance to hydrogenation under medium pressures. Hydrogenations at 600, 850, 1000 Bar and 1000 Bar with heating at 50 °C with 5% Pd-C, 5% Rh-C, 10% Pd-C and 10% Rh-C for 6 h all failed to give any quantifiable degree of hydrogenation. When the ethanol/acetic acid solvent and 5% Rh-Al_2O_3 catalyst system was employed, a hydrogenation at 400 PSI over 3 h at room temperature afforded a reaction mixture in which the substrate **118** had been completely consumed. T. L. C. analysis indicated that the mixture contained three hydrogenation products which were separated by dry flash chromatography; however, two were obtained in too small quantities for formal identification but showed a larger degree of saturation than the main hydrogenation product, 10b,11-dihydro-11-methyl-isoindolo[2,1-*a*]indol-6-one **349**, which was obtained in 80% yield (Scheme 114).



i : 5% Rh-Al_2O_3, 10:1 EtOH/AcOH, 400 PSI

Scheme 114

A second hydrogenation under the same conditions but with an extended reaction time (18 h) afforded the fully saturated 11-methyltetradecahydroisoindolo[2,1-*a*]indol-6-one **353** in 97% crude yield (Scheme 114) and suggests that all the benzopyrrolizinone systems could be fully hydrogenated if the reaction was run over a long enough time interval.

The hydrogenation experiments show that selective hydrogenation of the 1,2-bond of pyrrolo[1,2-*a*]indol-3-one **2** is possible under mild conditions affording the 1,2-dihydro derivative **96** as the major product (>95%). However, at high pressures there is no selectivity and a range of hydrogenation products are obtained although hydrogenation over a sufficient time interval may lead to the decahydro derivative **352** being obtained exclusively.

Pyrrolo[1,2-*a*]benzimidazol-1-one **280** is highly reactive, even in mild conditions, to hydrogenation giving the 1,2-dihydro derivative **350** and 2-ethylbenzimidazole **351** without selectivity.

Isoindolo[2,1-*a*]indol-6-one **3** affords the 10b,11-dihydro compound readily under mild conditions but the 11-methyl derivative **118** undergoes only minimal hydrogenation (<5%) under the same conditions. However, selective hydrogenation of **118** at high pressure, using rhodium-alumina catalyst, is possible and the 10b,11-dihydro and fully hydrogenated derivatives **349** and **353** can be obtained by controlling the duration of hydrogenation.

2.4.1.3 Solid state structure

Slow evaporation of toluene from isolated hydrogenation products afforded crystals suitable for structural determination by X-ray crystallography. The structure of 1,2,9,9a-tetrahydropyrrolo[1,2-*a*]indol-3-one **347** is shown in Figure 6 with the bond lengths and bond angles listed in Tables C and D (Appendix) and the structure of 10b,11-dihydroisoindolo[2,1-*a*]indol-6-one **348** is shown in Figure 7 with the bond lengths and bond angles listed in Table E (Appendix).

Comparison of the structures of the hydrogenation products **347** and **348** with the parent compounds **2** and **3** reveals several structural changes resulting from the hydrogenation. In both **347** and **348** there is lengthening of all the hydrogenated bonds relative to the parent compounds, particularly those which were formerly double bonds [*i.e.* in **2** C(9)-C(9a) 1.352(2) Å and in **347** C(9)-C(9a) 1.545(2) Å], and associated reduction in the exocyclic bond angles due to the change from sp^2 to sp^3 geometry of the carbon centres and therefore the planarity present in **2** and **3** is lost. The loss of planarity results in less nitrogen lone pair delocalisation into the ring system and this is shown by the C-N bond lengths which have values more typically associated with the usual amide delocalisation of the nitrogen lone pair to the carbonyl group [*i.e.* in **2** C(3)-N(4) 1.3937(18) Å and in **347** C(3)-N(4) 1.3596(19) Å whereas in tertiary γ-lactams C-N 1.344(14) Å].[89]

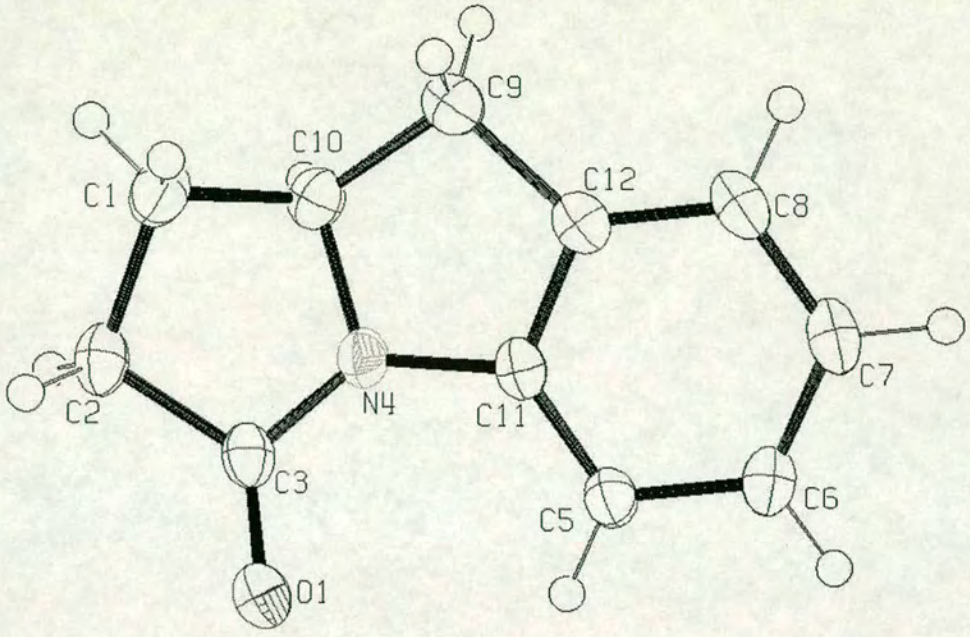


Figure 6 – crystal structure of 1,2,9,9a-tetrahydropyrrolo[1,2-*a*]indol-3-one **347**

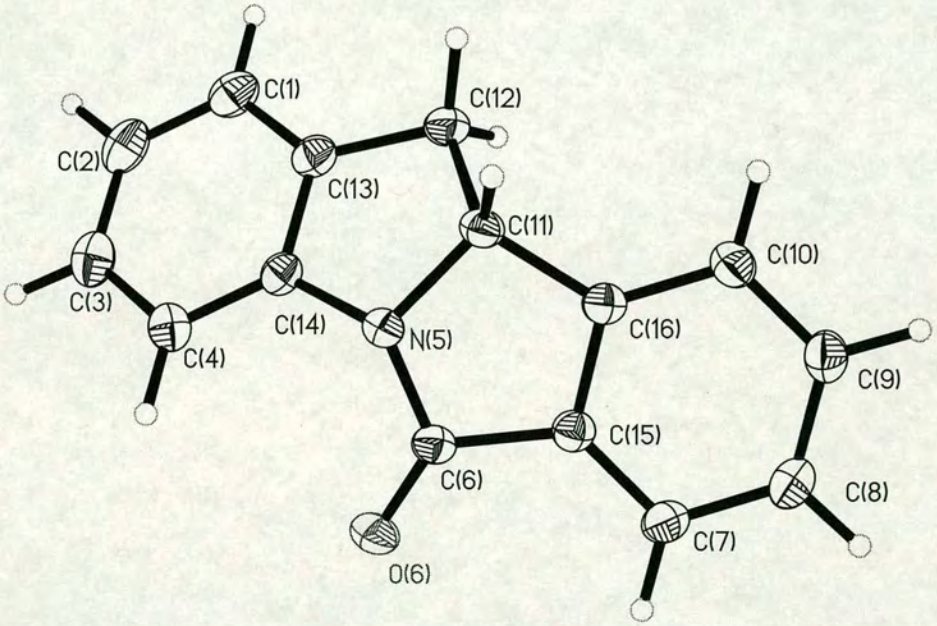


Figure 7 – crystal structure of 10b,11-dihydroisoindolo[2,1-*a*]indol-6-one **348**

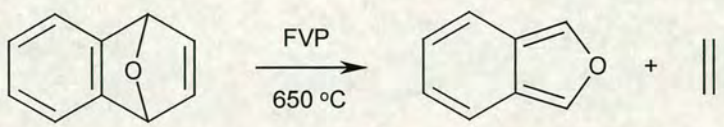
2.4.2 Pericyclic reactions

The 1,2-double bond of pyrrolizin-3-one **1** has previously been reported to react as the 2π-electron component in [4+2] Diels-Alder cycloaddition reactions with cyclopentadiene and isobenzofuran (benzo[*c*]furan) to form adducts which are predominantly the *endo* isomer.[44,48] 1,3-Dipolar cycloadditions across the 1,2-bond of **2** have been performed with a variety of azides to afford triazolines and reaction of **1** with ethoxycarbonylnitrile oxide generates a mixture of isoxazolines (section 1.2.5).[31,32,48]

Reactions of pyrrolo[1,2-*a*]indol-3-one **2** and pyrrolo[1,2-*a*]benzimiadzol-1-one **280** with both isobenzofuran **354** and cyclopentadiene **359** have been performed to establish any differences or similarities in the reactivity and the degree of stereochemical selectivity. A reaction of pyrrolo[1,2-*a*]indol-3-one **2** with 4-methoxybenzyl azide **364** has also been performed that establishes unequivocally the regiochemistry of the addition.

2.4.2.1 Diels-Alder [4+2] cycloaddition reaction with isobenzofuran

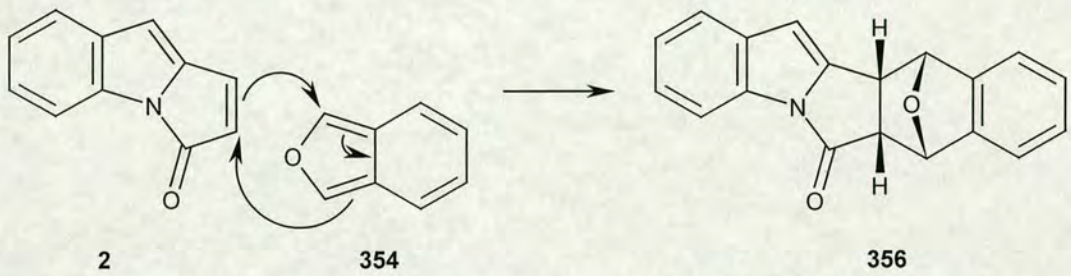
For the purposes of the cycloaddition reactions isobenzofuran **354** was generated immediately prior to use by flash vacuum pyrolysis of 1,4-epoxy-1,2,3,4-tetrahydronaphthalene **355**.[94] FVP was performed at 650 °C (using apparatus as described in section 3.2.9, Figure 15) and generated isobenzofuran **354** and ethylene *via* a retro Diels-Alder reaction (Scheme 115). However, isobenzofuran **354** is highly reactive and rapidly polymerises at room temperature so was collected as a white solid on a dry ice/acetone cold-finger trap whilst the ethylene side-product is removed by the vacuum to the subsequent liquid nitrogen trap.



355 **354**

Scheme 115

The isobenzofuran **354** was washed from the cold-finger, under nitrogen, with a minimum volume of ice-cold deuteriated acetone and immediately added to an ice-cold solution of pyrrolo[1,2-*a*]indol-3-one **2** in deuteriated acetone. The reaction mixture was allowed to warm to room temperature during which time the yellow colour of **2** faded. A proton NMR spectrum was recorded to allow calculation of the crude cycloadduct *endo*:*exo* ratio which indicated that a single isomer of product was present (>98%). The solvent was evaporated to afford crystalline 8,13-epoxy-7*a*,8,13,13*a*-tetrahydrobenzo[*f*]indolo[2,1-*a*]isoindol-7-one **356** in 92% yield (Scheme 116).



2 **354** **356**

Scheme 116

In a complementary experiment 1,4-epoxy-1,2,3,4-tetrahydronapthalene **355** and the indole *N*-propenoate precursor **308** were pyrolysed together at 925 °C using a cold-finger trap. The crude reaction products were washed from the trap, under nitrogen, with deuteriated acetone and it was immediately obvious that the reaction was not as clean (darker solution) as the addition of isobenzofuran **354** to previously isolated pyrrolo[1,2-*a*]indol-3-one **2**. However, analysis by proton NMR spectroscopy revealed that the cycloaddition generated the *endo* cycloadduct **356** only as previously observed. Purification of the crude product by recrystallisation from the minimum volume of isopropyl alcohol afforded only a 64% yield of isolated product.

The stereochemistry of the single isomer of adduct **356** was established by X-ray crystallography and is unequivocally the *endo* cycloadduct as shown in Figure 8 (Appendix, Table F).

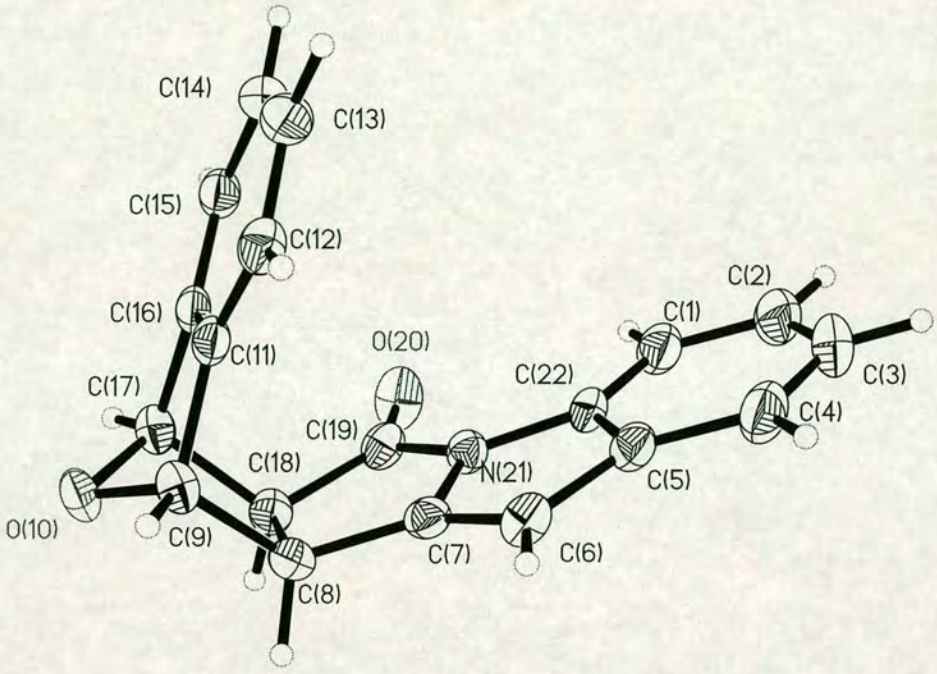


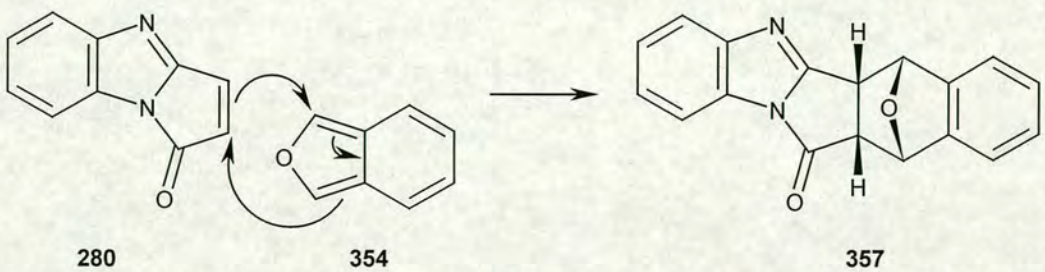
Figure 8 – *endo* isomer of cycloadduct **356**

The crystal structure clearly shows the 1,2-dihydrobenzopyrrolizinone and isobenzofuran moieties, joined by the new C(8)-C(9) and C(17)-C(18) bonds, lying on top of one another. Although the *endo* adduct is usually the less thermodynamically stable form of the two isomers, it is often the predominant isomer in many [4+2] cycloadditions. This is believed to be a result of the increased stabilisation of the *endo* transition state offered by favourable secondary orbital interactions. However, this type of favourable interaction is not present in the *exo* transition state and therefore no increased stabilisation is possible.[95] There is no significant loss of planarity of the 1,2-dihydrobenzopyrrolizinone moiety relative to benzopyrrolizinone **2** and the bond angle between the two aromatic units (i.e. benzene/indole) is 43.9°. The bond lengths of the 1,2-dihydrobenzopyrrolizinone moiety are not significantly different from those of comparative bonds in benzopyrrolizinone **2** or the tetrahydro derivative **347** except that the C(8)-C(18) in **356** is significantly longer [C(8)-C(18) is 1.557(2) Å whereas the equivalent bonds in **2** and **347** are 1.333(2) Å and 1.536(2) Å respectively]. This result is very similar to

that which has previously been observed for the cycloaddition of isobenzofuran **354** to pyrrolizin-3-one **1** in which the bond angle between the aromatic units (*i.e.* benzene/pyrrole) was 43.1° and planarity of the 1,2-dihydropyrrolizinone was maintained.

The generation of the *endo* isomer reflects the result of the adduct formation for the analogous reaction of pyrrolizin-3-one **1** with isobenzofuran but shows an even greater stereoselectivity than the 90:10 *endo/exo* mixture that was obtained in the reaction of pyrrolizin-3-one **1**.

The reaction of pyrrolo[1,2-*a*]benzimidazol-1-one **280** with isobenzofuran **354** proved to be much more troublesome. When freshly generated isobenzofuran **354** was washed from the cold-finger with deuteriated acetone and added to a freshly prepared solution of pyrrolo[1,2-*a*]benzimidazol-1-one **280** in deuteriated acetone the colour rapidly faded indicating that the reaction had occurred almost immediately to afford the cycloadduct **357** (Scheme 117). However, when general work-up techniques (dry flash chromatography and recrystallisation were used) to obtain a pure sample the crude product always appeared to degrade very quickly and no robust work-up method was achieved. However, a fortuitous recrystallisation from toluene afforded a few small crystals of 8,13-epoxy-7*a*,8,13,13*a*-tetrahydro-benzo[*f*]benzimidazo[2,1-*a*]isoindolo-7-one **357** of high purity suitable for full analysis and structural determination by X-ray crystallography.



280 **354** **357**

Scheme 117

The proton NMR spectrum of the adduct **357** showed only one isomer to be present and an X-ray crystal structure, shown in Figure 9 (Appendix, Table G), allowed unambiguous assignment of **357** as the *endo* isomer. The structure is very similar to that of **356** with the 1,2-dihydro-azabenzopyrrolizinone and isobenzofuran moieties lying on top of each other with a bond angle between the two aromatic units (*i.e.* benzimidazole and benzene) of 45.4°. The 1,2-dihydro-azabenzopyrrolizinone is planar and the longest bond is the C(8)-C(18) at 1.5560(16) Å and these two characteristics are very similar to those in the analogous adduct **356** obtained from the reaction of **2** with isobenzofuran.

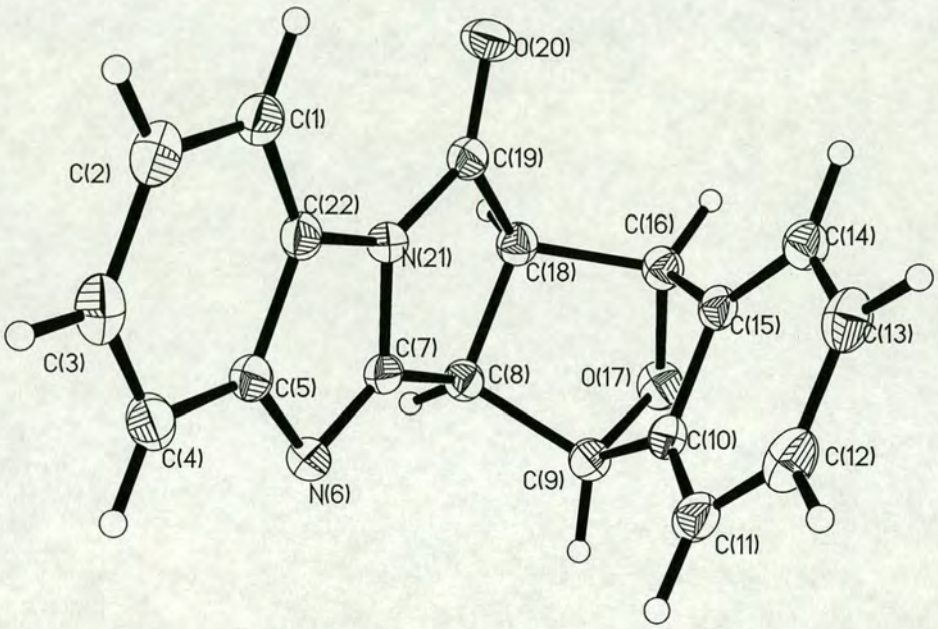


Figure 9 – *endo* isomer of cycloadduct **357**

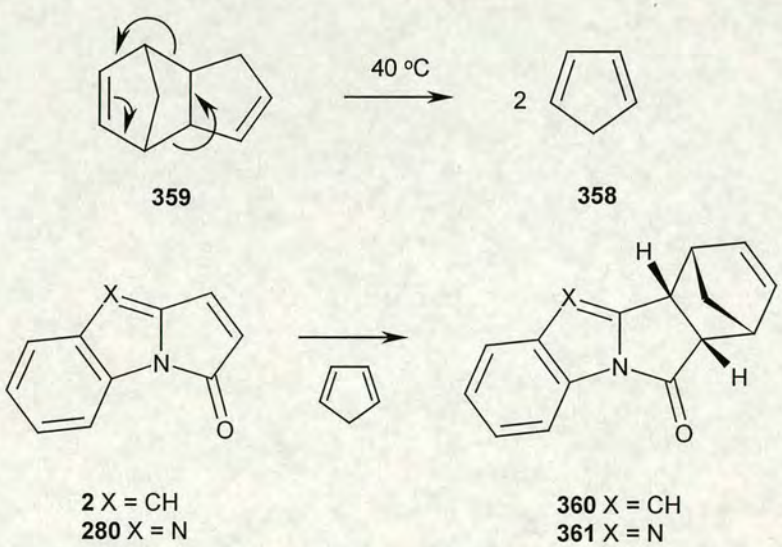
2.4.2.2 Diels-Alder [4+2] cycloaddition reaction with cyclopentadiene

For the cycloaddition it was necessary to generate cyclopentadiene **358** by thermal cracking of dicyclopentadiene **359**.

A solution of pyrrolo[1,2-*a*]indol-3-one **2** in acetone was treated with cyclopentadiene and left to stand for 1 h during which time the initial bright yellow colour faded. The excess cyclopentadiene and solvent were removed under vacuum

and the crude product purified by hot filtration and recrystallisation from hexane to afford the cycloadduct, 8,11-methano-7*a*,8,11,11*a*-tetrahydro-indolo[2,1-*a*]isoindolo-7-one **360**, in 92% yield (Scheme 118).

The reaction of pyrrolo[1,2-*a*]benzimidazol-1-one **280** with cyclopentadiene proved much less problematic than the reaction with isobenzofuran but precautions were taken to use as mild conditions as possible to minimise any degradation that may have occurred. The reaction was performed in the minimum volume of deuteriated acetone (0.5 cm^3) in order to obtain NMR spectra as quickly as possible. Upon addition of the cyclopentadiene the colour of the solution faded over 5 min and NMR spectra were obtained after which the excess reagent and solvent were removed *in vacuo* using a high capacity (FVP) pump (0.02 mmHg) to give 8,11-methano-7*a*,8,11,11*a*-tetrahydro-benzimidazo[2,1-*a*]isoindol-7-one **361**, in 90% crude yield (Scheme 118).



Scheme 118

A proton NMR spectrum of the adduct indicated a single isomer was present (>98%). The *endo* geometry of the cycloadduct **360** was assigned by comparison of the proton NMR spectrum with that of the analogous *endo* cycloadduct **192** formed from the addition of cyclopentadiene to pyrrolizinone **1**.[48] The aliphatic ring-junction protons of *endo* **192** are found at higher chemical shift than those of the *exo* isomer (*endo*: δ_H

3.57 ppm and δ_H 3.69 ppm, *exo*: δ_H 2.98 ppm and δ_H 3.14 ppm) and the coupling constants with the adjacent aliphatic protons are much larger in the *endo* isomer (*J* 4.3 Hz) than the *exo* isomer (*J* 1.2 Hz). The aliphatic ring-junction protons of **360** were identified by inspection at δ_H 3.57 ppm and δ_H 3.69 ppm and show characteristic coupling constants with the adjacent aliphatic protons of 4.3 Hz which is consistent with the *endo* isomer.

This result, like that of the reaction of **2** with isobenzofuran, affords an even greater degree of stereoselectivity than in the analogous reaction of pyrrolizin-3-one **1** with cyclopentadiene which gives a 95:5 mixture of *endo* and *exo* isomers respectively.

A crystallisation of the cycloadduct **360** by slow evaporation of the deuteriated chloroform NMR solvent afforded suitable crystals for structural determination by X-ray crystallography. The structure of **360** is shown in Figure 9 (bond length/angle data given in Appendix, Table H) and clearly showed the *endo* geometry with the C(12)-C(13) bond lying on top of the benzopyrrolizinone moiety.

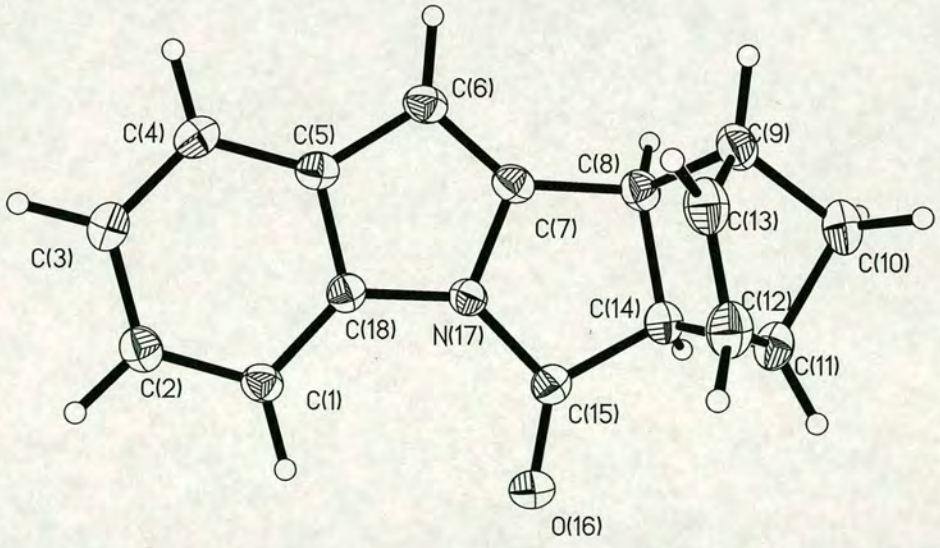


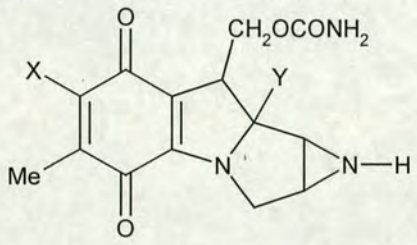
Figure 10 – *endo* isomer of cycloadduct **360**

The proton NMR spectrum of **361** at 360 MHz showed a two proton multiplet at δ_H 4.00-3.77 ppm for the two aliphatic ring-junction protons which could not be

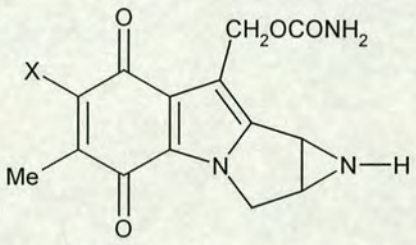
resolved. However, the similar chemical shift of the resonances to those of the equivalent protons in **360** and the exclusive formation of *endo* adducts in the previous instances strongly suggests that **361** is the *endo* isomer too.

2.4.2.3 1,3-Dipolar cycloaddition with 4-methoxybenzyl azide

Mitomycins **362**, and aziridinomitosenes **363**, are a class of antibiotics with a wide range of antibacterial and anti-tumour activity and hence pyrrolo[1,2-*a*]indol-3-one **2**, similar in structure to these antibiotics, is a candidate for further development for the direct synthesis of mitomycins and aziridinomitosenes.[30]



362

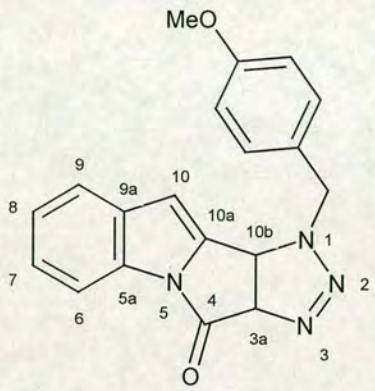


363

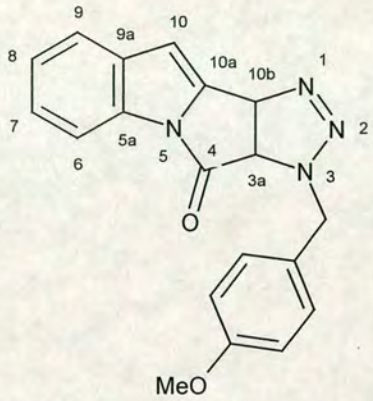
Franck and Auerbach have shown, during investigations into mitomycin synthesis, that the 1,2-bond of pyrrolo[1,2-*a*]indol-3-one **2** readily undergoes 1,3-dipolar addition of azides. However, technological limitations meant that it was not possible to prove the regiochemistry and the assignment was made using precedents from Huisgen's work on dipolar additions of azides to dipolarophilic double bonds conjugated with carbonyls.[32] Establishment of the regiochemistry is now possible using NMR techniques.

Initially it was intended to perform the 1,3-dipolar addition with trimethylsilyl azide since the trimethylsilyl function can be easily removed with aqueous acid to afford a *N*-unsubstituted 1,2,3-triazolo derivative. Pyrrolo[1,2-*a*]indol-3-one **2** and trimethylsilyl azide were added together in acetone and heated at 75 °C for 24 h but a proton NMR spectrum indicated that no reaction had occurred. In hindsight this is not surprising since trimethylsilyl azide is usually used for azidonation reactions not 1,3-dipolar additions. Re-evaluation suggested that 4-methoxybenzyl azide **364** was a more suitable azide for the 1,3-dipolar addition to pyrrolo[1,2-*a*]indol-3-one **2** since

methoxybenzyl can be used as a protecting group and its removal, after aziridine formation, would afford a proton in the correct position as in **362** and **363**. It was also clear that a NOESY NMR spectrum would show either correlation between the H-10 proton and benzyl resonances (for the adduct **365**) or correlation between the H-3a proton and benzyl resonances (for the adduct **366**) therefore establishing the regiochemistry.

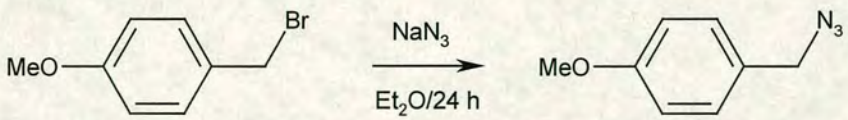


365



366

4-Methoxybenzyl azide **364** was prepared by the addition of sodium azide to a stirred solution of 4-methoxybenzyl bromide in DMF. After stirring at room temperature for 24 h the organic material was extracted with diethyl ether and dried over magnesium sulfate. Removal of the ether at the lowest possible temperature afforded 4-methoxybenzyl azide **364** as a colourless oil in 93% yield (Scheme 119).

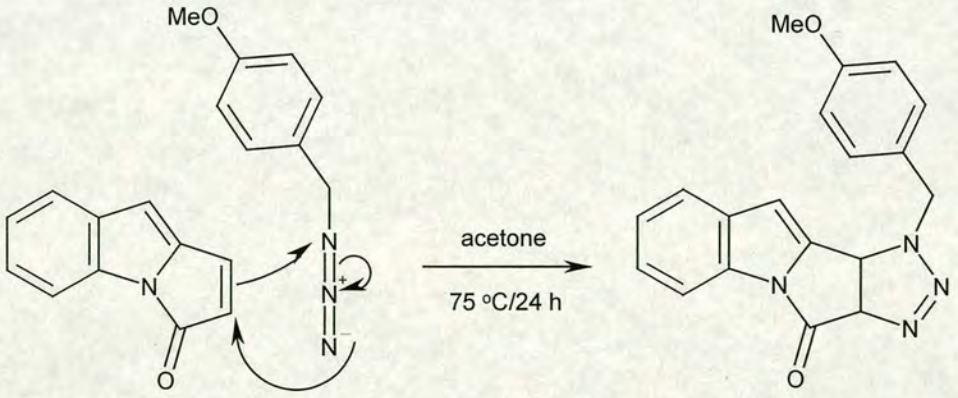


364

Scheme 119

The azide **364** was added dropwise to a stirred solution of pyrrolo[1,2-*a*]indol-3-one **2** in acetone and heated at 75 °C for 24 h during which time a precipitate formed. The reaction was concentrated to ~1 cm^3 then cooled at –20 °C overnight before being filtered and washed with a small quantity of ethyl acetate to give the azide adduct.

Inspection of the proton NMR spectrum allowed identification of the key proton resonances for establishment of the regiochemistry. The H-10 signal at δ_H 6.51 ppm exhibits only long range coupling (*J* 0.6 Hz) whereas the benzyl methylene protons, doublets at δ_H 5.04 ppm and δ_H 4.79 ppm (*J* 14.8 Hz), have similar chemical shifts and coupling constant to reported cyclic triazolines (*e.g.* 1-benzyl-10-methoxymethyl-3a,10b-dihydro-[1,2,3]triazolo[4',5':3,4]pyrrolo[1,2-*a*]indol-4-one; δ_H 5.31 ppm and δ_H 4.86 ppm, *J* 16 Hz).[32] The H-3a ring junction proton shows a doublet at a high chemical shift of δ_H 5.93 ppm (*J* 10.5 Hz) due to the deshielding effect of the adjacent nitrogen and carbonyl moieties and comparison of the coupling constant gives the second ring junction proton, H-10b, as a doublet at δ_H 4.98 ppm (*J* 10.5 Hz). A NOESY NMR experiment (Figure 11) was performed that shows key correlations of the H-10 proton with the H-10b ring junction proton and the benzyl methylene proton at δ_H 4.79 ppm. There is no correlation of the benzyl methylene protons with the H-3a ring junction proton, ruling out the regiochemistry of the adduct **366**. Therefore unambiguous assignment of the regiochemistry of the adduct as 1-(4-methoxybenzyl)-3a,10b-dihydro-[1,2,3]triazolo[4',5':3,4]pyrrolo[1,2-*a*]indol-4-one **365** is possible (Scheme 120).



2 **364** **365**

Scheme 120

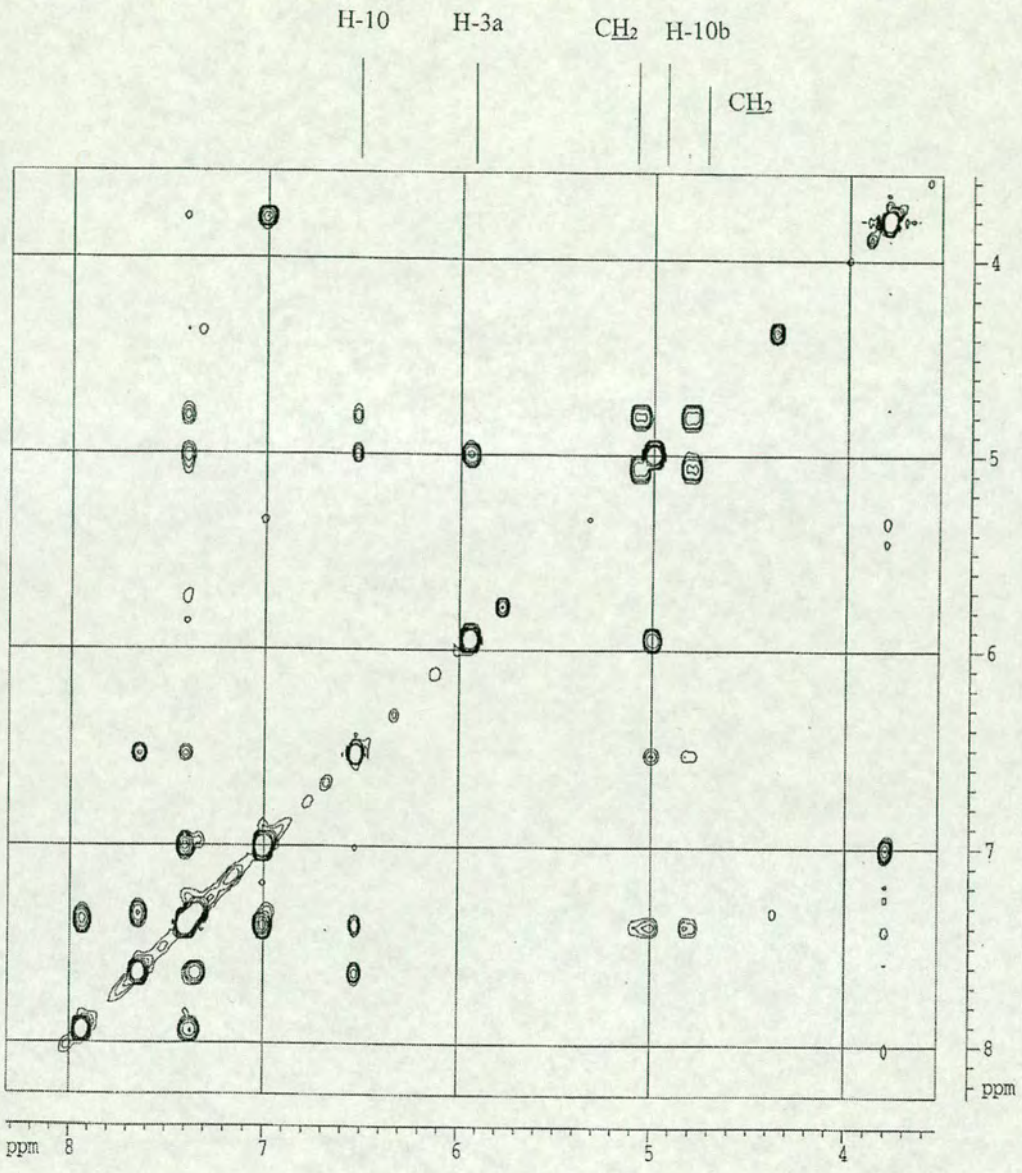


Figure 11 – NOESY NMR spectrum of **365**

The successful reaction of pyrrolo[1,2-*a*]indol-3-one **2** with 4-methoxybenzyl azide has allowed establishment of the regiochemistry of azide addition to benzopyrrolizin-3-ones and, perhaps more importantly, gives a three step route to the key precursor **365** in mitomycin synthesis in 80% overall yield. Further progress towards the mitomycin skeleton could be achieved by:

i) aziridine formation by nitrogen elimination from triazolo derivatives which has been demonstrated by Franck and Auerbach using photolysis at wavelengths below 310 nm.[31]

ii) removal of the methoxybenzyl protecting group using aqueous acid to afford an *N*-unsubstituted aziridine

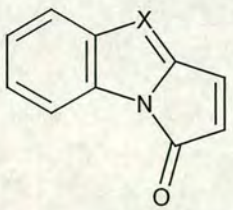
iii) reduction of the carbonyl by ring-opening with lithium aluminium hydride with appropriate protection of the aziridine.

2.4.3 Reactions with nucleophiles

The reactions of pyrrolizinone **1** with nucleophiles are discussed in section 1.2.3. However, there is very little reported for the reaction of the benzopyrrolizinone **2**, azabenzopyrrolizinone **280** or isoindoloindolone **3** systems with nucleophiles (section 1.2.3). Like pyrrolizinone these systems have the potential for reaction of 'hard', 'soft' and 'intermediate' nucleophiles at the 'hard' carbonyl and/or the 'soft' enone electrophilic centres.

2.4.3.1 Reactions with a *H*-nucleophile

Lithium aluminium hydride has been used as a source of H^- to effect ring-opening of pyrrolo[1,2-*a*]indol-3-one **2** and pyrrolo[1,2-*a*]benzimidazol-1-one **280** with a varying degree of success.



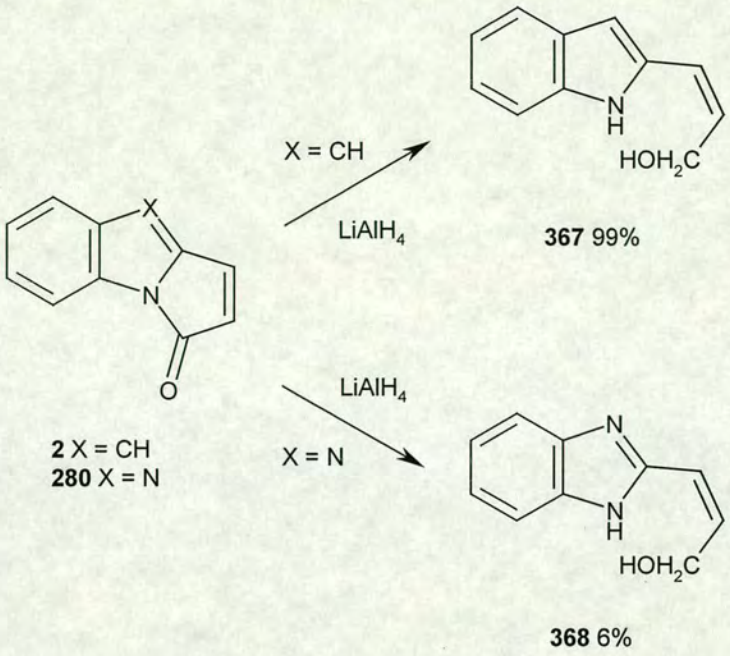
2 X = CH
280 X = N

The reduction was performed using the same conditions for each substrate: a solution of the substrate in dry ether was added dropwise to a suspension of lithium aluminium hydride in dry ether under nitrogen at such a rate as to produce gentle reflux. In the reaction of **2** the mixture was heated under reflux for 30 min upon completion of the addition, during which time decolourisation occurred. No such heating was necessary in the reaction of **280** since decolourisation occurred readily at

room temperature over 15 min which is perhaps not surprising considering the likely increased reactivity of the amide moiety in **280** due to the electron withdrawing effect of the additional nitrogen atom.

The method of work-up involved the addition of wet ether followed by water then an aqueous solution of potassium tartrate to the reaction and vigorous shaking before filtration through a pad of celite to remove the precipitated salts. Separation of the ether layer and extraction of the aqueous phase with three further portions of ether followed by drying over $MgSO_4$ and removal of the ether *in vacuo* afforded the alcohol ring-opened product of **2**, *cis*-3-(indol-2-yl)-prop-2-en-1-ol **367**, in quantitative yield (Scheme 121). However, this was not the case for the reaction with **280** and the work-up proved particularly difficult. Under the same method no ring-opened product was recovered. The problem is likely to be the amphoteric nature of the ring-opened benzimidazole moiety. An adapted work-up method was used in which wet ether, water and a solution of potassium tartrate were added and the solution shaken vigorously before filtration through a pad of celite. The solution was adjusted to pH 7 then continually extracted into DCM for 48 h after which organic extracts were concentrated and absorbed onto silica. Dry flash chromatography separated side-products and the highly polar ring-opened product was washed off the column with methanol. The crude product was concentrated to ~1 cm^3, filtered through a celite pad to remove traces of silica and the solvent allowed to evaporate to dryness at atmospheric pressure whereupon crystallisation occurred. The product was washed with acetone (5 drops) at the water pump to give *cis*-3-(benzimidazol-2-yl)-prop-2-en-1-ol **368** in just 6% yield (Scheme 121).

Several more reductions were performed and small changes in the work-up attempted: firstly the pH was adjusted slightly to be very mildly acidic or basic and then in another attempt, after the initial addition of the wet ether, water and potassium tartrate solution, the entire reaction mixture was extracted for 48 h without filtration to remove the precipitated salt but to no avail. No improvement could be made on the 6% yield of **368**.



Scheme 121

The products of the reductive ring-opening are exclusively of the (*Z*)-configuration and were identified by ^{1}H NMR, ^{13}C NMR spectroscopy and mass spectroscopy.

In the proton NMR spectrum the chemical shifts and the splitting patterns of the propenol moiety of **367** and **368** are very similar to those of the analogous pyrrole derivative, *cis*-3-(imidazol-2-yl)-prop-2-en-1-ol **238** (Table 20).[96] The C-1 methene protons occur as a two proton double doublet whilst the C-2 methine proton signal is a double triplet resulting from splitting by the C-1 protons and the C-3 methine proton which is itself a doublet. The coupling constant of ~12 Hz between the C-2 and C-3 protons of the propenol is similar to the coupling constants of (*Z*)-propenoate precursors and confirms the *cis*-geometry of the double bond.

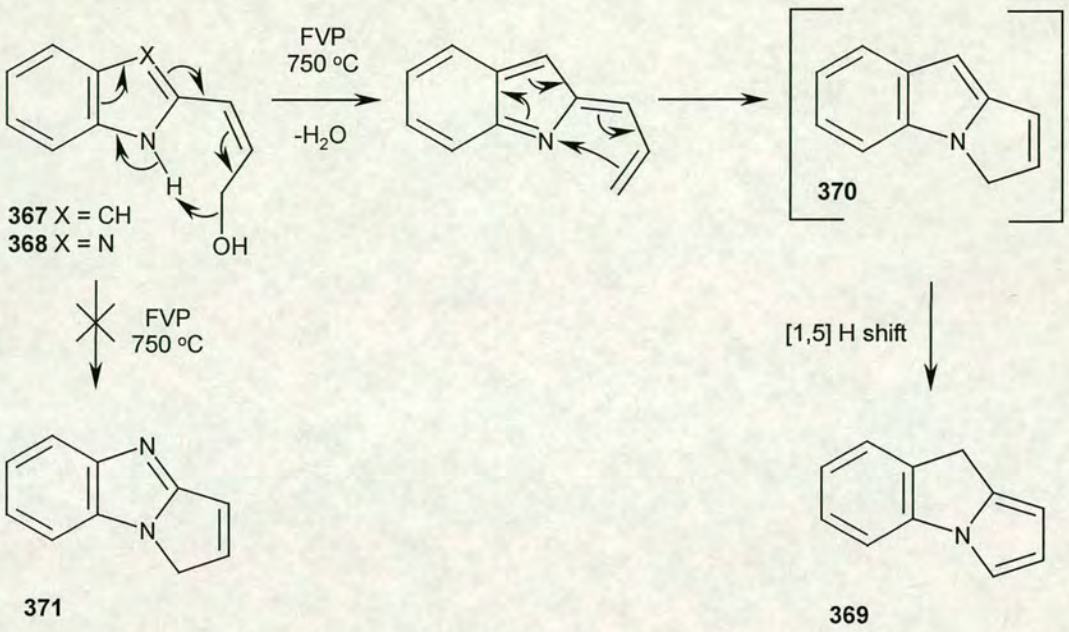
Compound	δ_H/ppm			δ_C/ppm (CH_2)
	(2)H-1 (Hz)	H-2 (Hz)	H-3 (Hz)	
238	4.35 (*J* 5.7)	6.01 (*J* 12.1, 5.7)	6.39 (*J* 12.1)	58.64
367	4.34 (*J* 6.4)	5.77 (*J* 12.0, 6.4)	6.54 (*J* 12.0)	59.29
368	4.54 (*J* 5.3)	6.09 (*J* 11.9, 5.3)	6.28 (*J* 11.9)	59.34

Table 20 – 1H chemical shifts and coupling constants of the propenol moiety

The ^{13}C NMR spectra clearly show a CH_2 signal in each case and its chemical shift also serves to indicate the formation of a primary alcohol. Mass spectrometry gave molecular ions (M^+) at *m/z* 173 and 174 for **367** and **368** respectively.

This is a useful method of ring-opening that provides a regiospecific 3-step route to the *cis*-2-alcohol **367** in 85% overall yield from indole. If a similar yield of **368** is to be obtained then optimised work-up conditions must be found.

A pyrolysis of *cis*-3-(indol-2-yl)-prop-2-en-1-ol **367** was performed at 750 °C and gave 9*H*-pyrrolo[1,2-*a*]indole **369** as the sole product in 91% yield by rearrangement of the initially formed 3*H*-pyrrolo[1,2-*a*]indole **370** (Scheme 122). 9*H*-Pyrrolo[1,2-*a*]indole **369** was identified by comparison of NMR spectra with authentic data.[97] This result indicates that the substrate **367** was of (*Z*)-configuration and affords a useful synthesis of the 9*H*-pyrrolo[1,2-*a*]indole **369** in four steps from available starting materials in 77% overall yield.

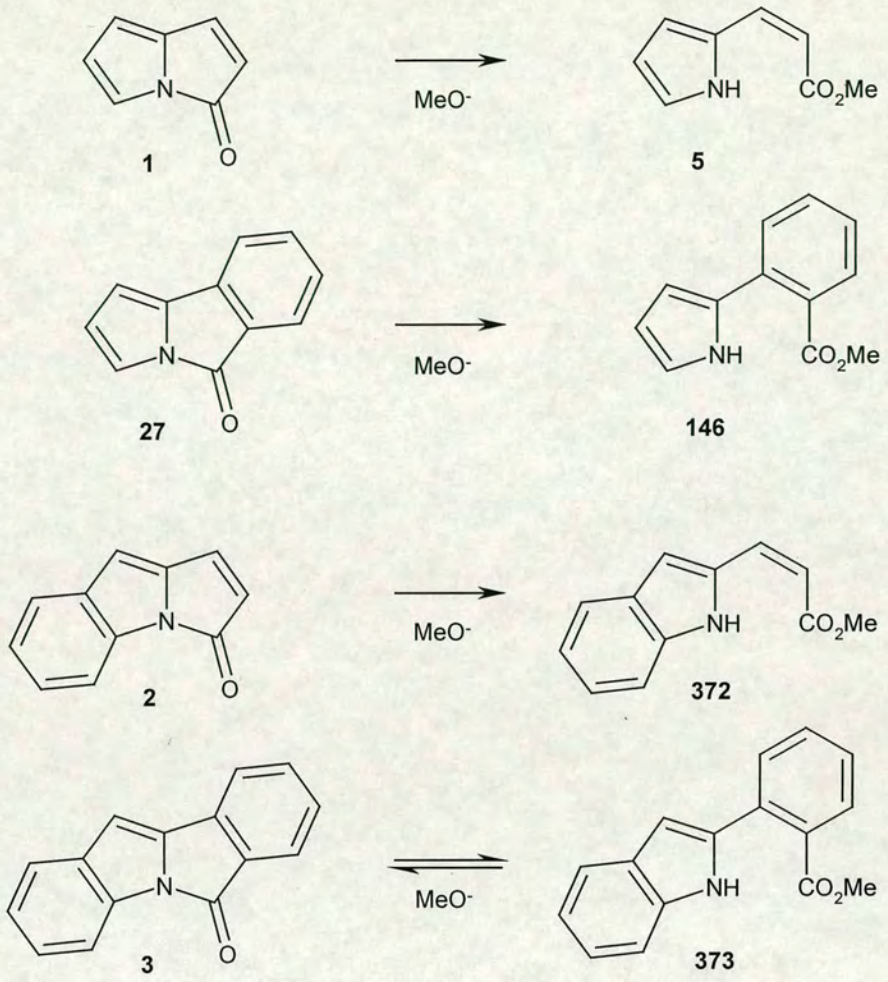


Scheme 122

Unfortunately 4*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazole **371** was not obtained under similar repyrolysis conditions due to the very low volatility of *cis*-3-(benzimidazol-2-yl)-prop-2-en-1-ol **368** (Scheme 122).

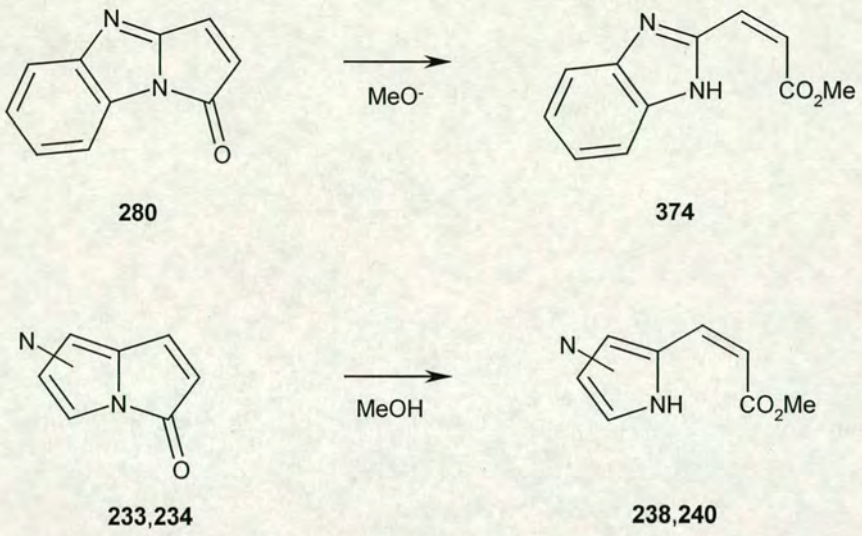
2.4.3.2 Reactions with an *O*-nucleophile

Treatment of pyrrolo[1,2-*a*]indol-3-one **2** with a solution of diisopropylethylamine in methanol at room temperature caused decolourisation over 2.5 h and afforded *cis*-3-(indol-2-yl)-acrylic acid methyl ester **372** in 93% yield after removal of the solvent (Scheme 123). Complete ring-opening at the amide linkage under basic conditions has been readily obtained for pyrrolizin-3-one **1** and pyrrolo[2,1-*a*]isoindolo-5-one **27** to afford the *cis*-pyrrole 2-propenoate **5** and pyrrole 2-benzoate **146**.[50] However, methoxide ring-opening of isoindolo[2,1-*a*]indol-6-one **3** does not go to completion but instead reaches ~50:50 equilibrium mixture of the substrate, **3**, and the ring-opened indole 2-benzoate **373** (Scheme 123).[98] A tentative reason for this may be that the presence of two benzene rings increases the acidity of the indole nitrogen proton thus enabling recyclisation to the tetracycle **3** under basic conditions.



Scheme 123

The reaction of pyrrolo[1,2-*a*]benzimidazol-1-one under the same conditions as used for **2** was much more rapid. Complete decolourisation occurred in 5 min and returned *cis*-3-(benzimidazol-2-yl)-acrylic acid methyl ester **374** in near quantitative yield (Scheme 124). That the reaction should occur so quickly is perhaps not surprising considering that the pyrroloimidazol-5-ones **233** and **234** have been shown to undergo rapid ring-opening in neutral methanol at room temperature.[48]



Scheme 124

The products are exclusively of the (*Z*)-configuration and were identified from ^{1}H NMR, ^{13}C NMR and mass spectroscopy. The proton NMR spectrum of **372** shows no indole H-2 resonance, unlike the indole 3-propenoate **298** and indole *N*-propenoate **308** [δ_H 8.82 ppm and δ_H 8.46 ppm for the (*Z*)-isomers of **298** and **308** respectively], which confirms the presence of the propenoate chain in the 2-position. The propenoate has similar characteristics to those of **298** and **308** and has a coupling constant of 12.6 Hz between the olefinic resonances therefore indicating the (*Z*)-configuration of propenoate double bond. Similar comparisons can be drawn between the proton NMR spectra of the benzimidazole *N*-propenoate **291** and the ring-opened benzimidazole 2-propenoate **374**. There is no benzimidazole H-2 resonance in the latter and the propenoate olefinic coupling constant is 12.8 Hz which confirms the regiochemistry of **374** and the regiospecificity of its formation.

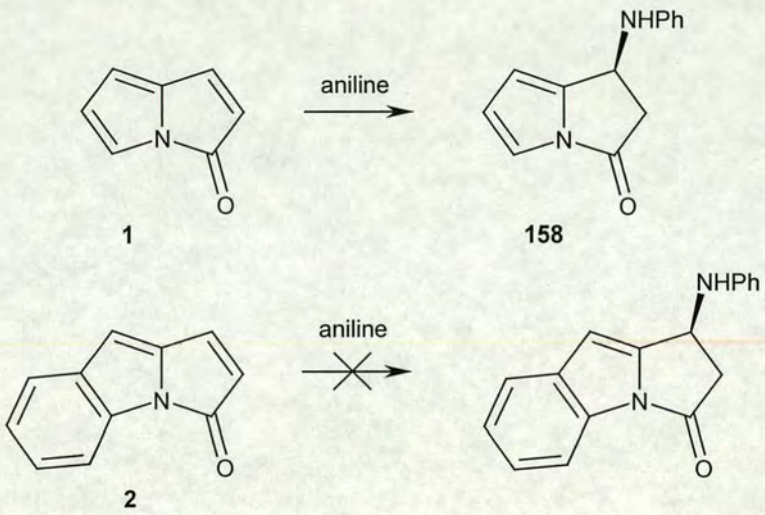
The 'hard' character of the methoxide ion, like that of hydride ion from $LiAlH_4$, affords reaction solely at the 'hard' carbonyl carbon and gives a largely general route for obtaining the stereospecific *cis*-2-substituted products in good overall yields in just three steps from starting materials.

2.4.3.3 Reactions with *N*-nucleophiles

The intermediate 'hardness' of amines gives the potential for reaction at the 'hard' carbonyl carbon or 'soft' enone 1-position. A series of experiments was performed to establish any pattern in the formation of products and any similarities/dissimilarities with the pyrrolizin-3-one system **1**.

2.4.3.3.1 Reactions with primary amines

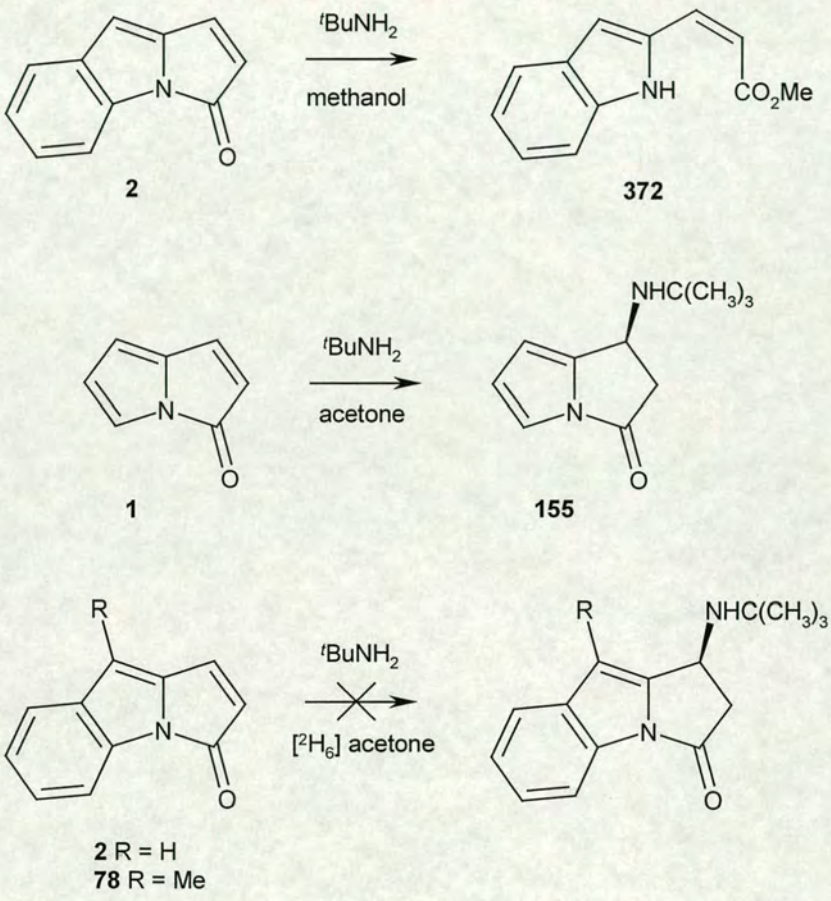
Pyrrolo[1,2-*a*]indol-3-one **2** in acetone was added to a suspension of aniline in water and heated under reflux for 9 h in accordance with a literature procedure.[48] Such forcing conditions are required due to the low nucleophilic reactivity of aniline and in this instance no reaction was observed. The recovery of **2** from the reaction is in contrast to the analogous reaction with pyrrolizin-3-one **1** which afforded a 68% yield of the 'Michael' adduct **158** (Scheme 125).[48]



Scheme 125

The reaction of pyrrolo[1,2-*a*]indol-3-one **2** with *tert*-butylamine in methanol afforded only the ring-opened (*Z*)-propenoate **372** which was identified by comparison of the proton NMR spectrum with authentic data (section 3.9). Formation of the propenoate **154** is also observed for the same reaction with pyrrolizinone **1** but when the reaction was performed in acetone over 48 h the 'Michael' adduct **155** was obtained exclusively in 61% yield.[48] At this point a switch

to 'NMR tube' scale reactions was made. This was advantageous since it allowed reactions to be performed on a small-scale and for the course of the reactions to be monitored by proton NMR spectroscopy. Reaction were performed in deuteriated acetone and involved treatment of pyrrolo[1,2-*a*]indol-3-one **2** and 9-methylpyrrolo[1,2-*a*]indol-3-one **78** with *tert*-butylamine under similar conditions but no products were formed after 72 h (Scheme 126).

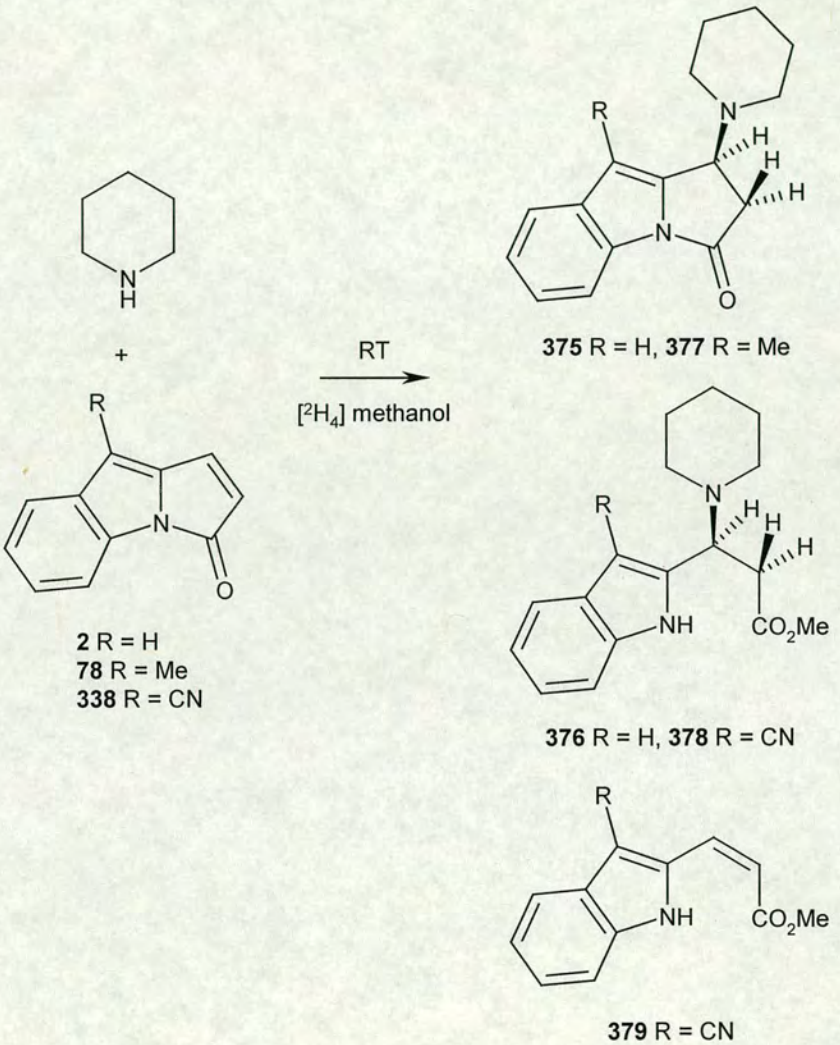


Scheme 126

2.4.3.3.2 Reaction with a secondary amine

Reactions of pyrrolo[1,2-*a*]indol-3-one **2** and its 9-methyl and 9-cyano derivatives **78** and **338** with piperidine were performed on an NMR tube scale using in both [$^2H_4$] methanol and [$^2H_6$] acetone as solvents. Product assignments were made on the basis of characteristic resonances observed in the proton NMR spectra.

The reaction of pyrrolizin-3-one **1** with piperidine proceeded smoothly over 45 min to afford the 'Michael' addition product **156** in 90% yield. However, the reactions of the benzopyrrolizinones **2**, **78** and **338** performed in [$^2H_4$] methanol gave varied results.

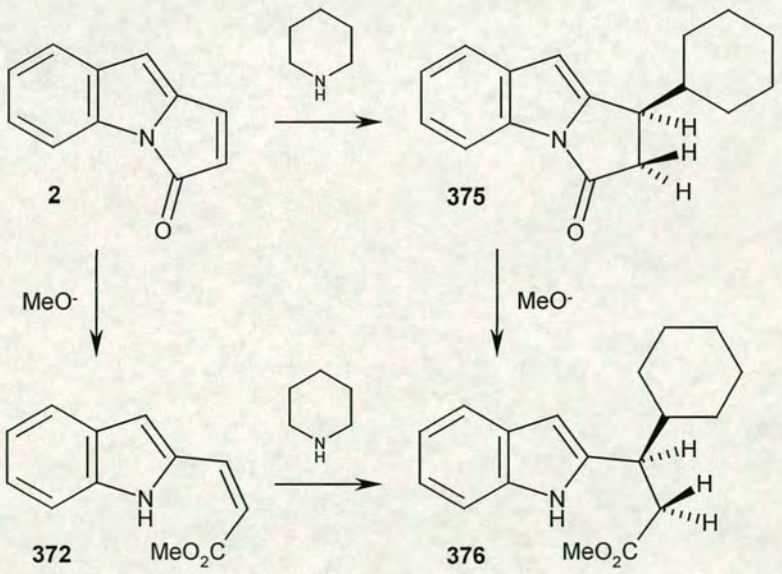


Substrate	R	Product(s)	Ratio
2	H	**375 376** ---	50:50
78	Me	**377** --- ---	100
338	CN	--- **378 379**	33:66

Scheme 127

The reaction of pyrrolo[1,2-*a*]indol-3-one **2** with piperidine in methanol afforded a 50:50 mixture of the 'Michael' adduct, 1,2-dihydro-1-piperidin-1-yl-pyrrolo[1,2-*a*]indol-3-one **375**, and the methoxide ring-opened adduct, 3-(indol-2-yl)-3-piperidin-1-yl propionic acid methyl ester **376**. 9-Methylpyrrolo[1,2-*a*]indol-3-one **78** did give exclusively the 'Michael' adduct **377** whereas 9-cyanopyrrolo[1,2-*a*]indol-3-one **338** failed to afford any adduct derived solely from 'Michael'-type conjugative addition but instead gave a 33:66 mixture of the methoxide ring-opened 'Michael' adduct **378** and the (*Z*)-propenoate **379** (Scheme 127).

The ring-opening observed in the reaction of **2** is caused by the presence of methoxide which is generated in small amounts by equilibrium deprotonation of methanol by the piperidine. That this reaction occurs, where it does not for the analogous reaction of pyrrolizinone **1**, may be a result of the reduced electron donation by the indole moiety of **2** relative to that of the pyrrole moiety in **1** hence activating the amidic bond towards cleavage by methoxide. Since no ring-opened product **372** is obtained, it suggests that the ring-opened adduct **376** is formed by initial conjugate addition followed by ring-opening by methoxide (Scheme 128).

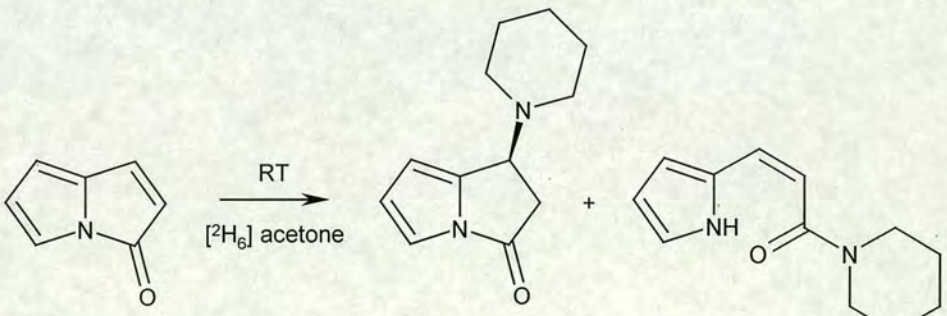


Scheme 128

The absence of methoxide ring-opening in the reaction of 9-methylpyrrolo[1,2-*a*]indol-3-one **78** with piperidine, to give either the ring-opened adduct or the (*Z*)-propenoate, is an unusual result which remains unexplained at present. The mild electron donating effect of the methyl substituent of **78** is unlikely be sufficient to stabilise the amide bond and prevent ring-opening by methoxide.

In the reaction of 9-cyanopyrrolo[1,2-*a*]indol-3-one **338** the rate of ring-opening by methoxide appears to be greater than that of addition of piperidine at the 1-position such that any of the 'Michael' adduct **380** formed is ring-opened to give **378**. The increased rate of reaction of methoxide at the carbonyl centre may be due to the strong electron withdrawing effect of the cyano substituent. That the (*Z*)-propenoate **379** does not appear to undergo addition of piperidine may be a result of reduced reactivity of the electrophilic centre due to the removal of ring strain, present in **338**, by ring-opening by methoxide.[48]

In acetone solution, the reaction of pyrrolizin-3-one **1** with piperidine affords a 74:26 mixture of 'Michael' adduct **156** and propenamide **157** (Scheme 129).

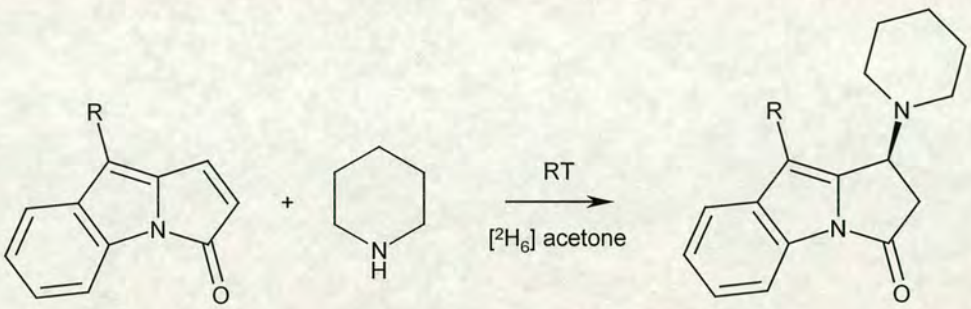


1 **156** **157**

Scheme 129

In stark contrast to the reaction of **1** the reactions of **2**, **78** and **338** with piperidine in [$^2H_6$] acetone afforded the 'Michael' adducts **375**, **377** and **380** exclusively, generally over a period of 1-1.5 h (Scheme 130). The result is unusual although no reaction conditions/duration was given for the reaction of **1** with piperidine in acetone.

Protonation of the anion generated by the initial addition is presumably by water dissolved in the acetone (since if it was protonated by [$^2H_6$] acetone then a deuterium would be present in the product) and so to get a meaningful comparison of the reactions of **1** and **2** a competitive reaction involving 1 equivalent of **1**, 1 equivalent of **2** and 2 equivalents of piperidine in acetone should be performed. This could be used to establish what products are formed and which reaction, if any, was faster.



2 R = H
78 R = Me
338 R = CN

375 R = H
377 R = Me
380 R = CN

Scheme 130

1,2-Dihydro-1-piperidinyl-pyrrolo[1,2-*a*]indol-3-one **375** was isolated and fully characterised. The proton NMR spectrum showed the three dihydro protons at δ_H 2.96 ppm (*J* 18.6 and 3.3 Hz), δ_H 3.17 ppm (*J* 16.6 and 8.3 Hz) and δ_H 4.39 ppm (*J* 8.3 and 3.3 Hz), the ^{13}C NMR spectrum a CH_2 resonance at 24.11 ppm and the mass spectrum gave the molecular ion at *m/z* 254. The 'Michael' adducts **377** and **380** were identified by the characteristic 1,2-dihydro proton NMR resonances found at ~3.0 ppm and mass spectroscopy. The 'Michael' adducts **377** and **380** were identified by the characteristic 1,2-dihydro proton NMR resonances and by the molecular ion peaks (M^+ 269 and MH^+ 280 respectively) in the mass spectra. For **380** the dihydro protons were identified at δ_H 2.90 ppm (*J* 15.6 and 3.9 Hz), δ_H 3.26 ppm (*J* 15.6 and 9.6 Hz) and δ_H 4.40 ppm (*J* 9.6 and 3.9 Hz). The H-2_{anti} and H-2_{syn} protons show large two-bond coupling with each other but can be identified by the three-bond couplings, 9.6 and 3.9 Hz respectively. However, the dihydro protons of **377** did not display similar splitting patterns to **375** but were identified in a 2:1 ratio at approximately δ_H 2.96 ppm and δ_H 4.45 ppm.

A crystal structure of 1,2-dihydro-1-piperidinyl-pyrrolo[1,2-*a*]indol-3-one **375**, shown in Figure 12 (bond length and bond angle data given in Appendix, Table I), was also obtained after fortuitous crystallisation of the adduct from the NMR solvent and shows unequivocally that addition has taken place at the 1-position of pyrrolo[1,2-*a*]indol-3-one **2**. The C(1)-C(2) bond length has increased from 1.333(2) Å in **2** to 1.5480(17) Å in **375** and this result is similar to the increase in bond length observed upon hydrogenation of **2** as observed for the tetrahydro derivative **347** [C(1)-C(2) 1.536(2) Å] (section 2.4.1.2).

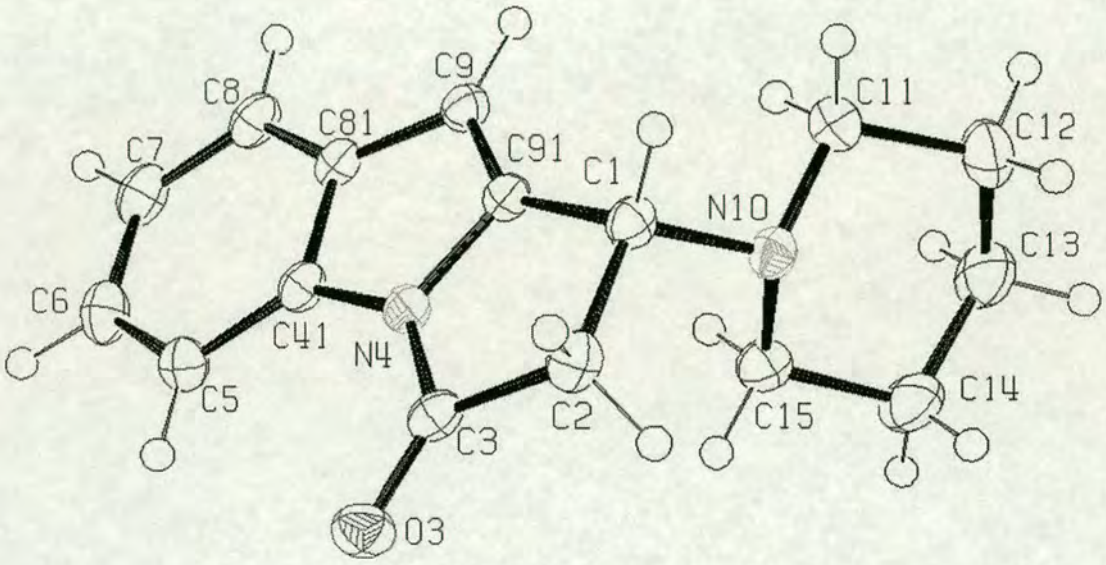
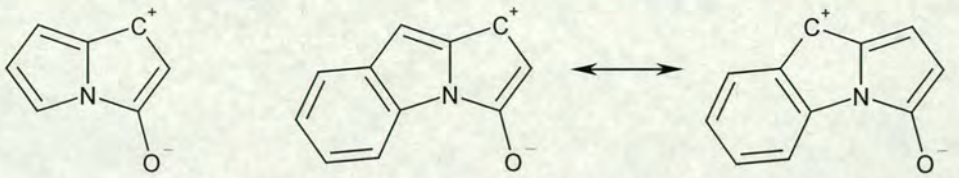


Figure 12 – crystal structure of 'Michael' adduct **375**

When addition of amines occurs it appears to be solely at the enone C(1) position with no ring-opening addition to form propenamides being observed in methanol or acetone. The results of reactions with amines vary greatly from the analogous reactions of pyrrolizin-3-one **1**, indeed the only conditions for which the same result occurs is the ring-opening with *tert*-butylamine in methanol. The C(1) position seems to be less reactive towards nucleophilic attack by amines relative to **1**. In **1** the nitrogen lone pair can be delocalised around the pyrrole ring to form a 6π-system of high electron density that has an adjacent enone system in which the δ^+ polarisation is solely at the C(1)-position. However, in **2** the benzene ring has the potential to draw electron density away from the pyrrole ring that may result in a lower aromatic

and increased enamine character of the 9-9a double bond. This would generate a dienone system in which the δ^+ polarisation is spread over two centres therefore reducing activity towards nucleophiles relative to **1**.



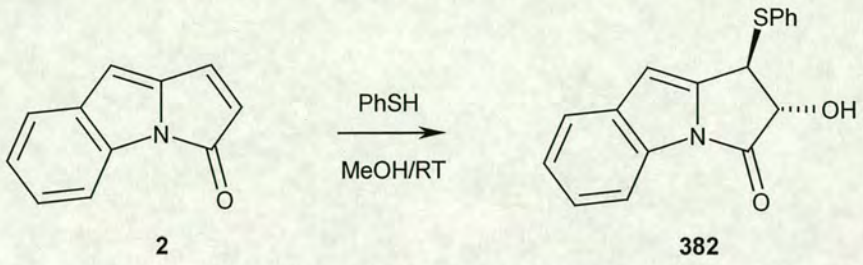
1a **2a** **2b**

The reaction of piperidine with pyrrolo[1,2-*a*]indol-3-one **2** in methanol affords methoxide ring-opening to give a mixture of 'Michael' adduct/methoxide ring-opened adduct whereas the reaction in acetone gives solely 'Michael' adduct. The results of reactions with piperidine contrast with those found for pyrrolizinone **1** where it appears that the 'Michael' adduct is obtained exclusively in methanol and a 'Michael' adduct/ring-opened propenamide mixture is obtained in acetone although this needs further clarification.

2.4.3.4 Reactions with an *S*-nucleophile

Thiophenol was selected as a suitable 'soft' *S*-nucleophile and as such was expected to undergo addition at the 'soft' C(1) electrophilic centre.

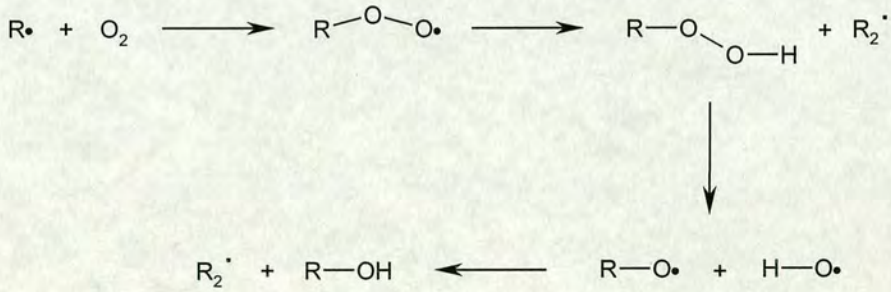
The reaction of pyrrolo[1,2-*a*]indol-3-one with thiophenol was initially performed in methanol, the same conditions as used for the reaction of thiophenol with pyrrolizin-3-one **1**. Unlike other addition reactions in which the initial colour fades, the reaction became dark in colour. A proton NMR spectrum indicated complete consumption of the substrate, however, only two of the three aliphatic protons that were expected for the addition product **381** (shown in Scheme 133) could be identified. The ^{13}C NMR spectrum indicated that there was no CH_2 moiety present but T. L. C. analysis showed only one major product. A dry flash column was performed using 20% ethyl acetate in hexane to isolate the product (32% yield) that was subsequently characterised by NMR spectroscopy and mass spectroscopy and identified as 1,2-dihydro-1-phenylthio-2-hydroxy-pyrrolo[1,2-*a*]indol-3one **382** (Scheme 131).



2 **382**

Scheme 131

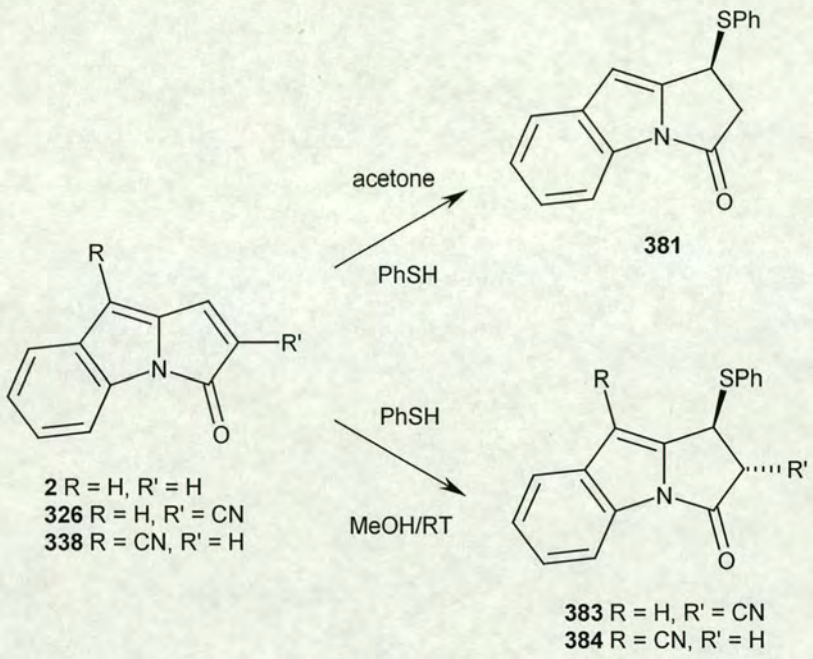
It is not clear why **382** is obtained when the analogous reaction with **1** to provide the 'Michael' adduct is fast and clean. Inspection of the three-bond coupling constant, 3.4 Hz, and comparison with the unambiguously assigned $^{3}J_{1,2}$ *anti* and *syn* coupling (7.9 and 2.8 Hz) in 1,2-dihydro-1-phenylthiopyrrolizin-3-one **166** (section 1.2.3.3) indicated that the *anti* diastereomer had been formed.[48] It is a very unusual result although it has been found to be reproducible. It may be that **382** is undergoing an autoxidation as shown below although it is not clear how it may be initiated (Scheme 132).



Scheme 132

Having previously found that the addition of piperidine to pyrrolo[1,2-*a*]indol-3-one **2** was successful in acetone solution, the same conditions were applied to the thiophenol addition. Addition of thiophenol to a solution of pyrrolo[1,2-*a*]indol-3-one **2** in acetone resulted in decolourisation over 5 min and gave the addition product 1,2-dihydro-1-phenylthio-pyrrolo[1,2-*a*]indol-3one **381** was isolated in 92% yield after purification by dry flash chromatography (Scheme 133). Characteristic aliphatic

proton resonances were identified at δ_H 4.77 ppm (*J* 8.2 and 3.1 Hz), δ_H 3.44 ppm (*J* 18.7 and 8.2 Hz) and δ_H 3.00 (*J* 18.7 and 3.1 Hz) in the ^{1}H NMR spectrum as well as the CH_2 resonance at δ_C 43.19 ppm in the ^{13}C NMR spectrum.



Scheme 133

In contrast to the reaction of **2** in methanol, the reactions of 2-cyanopyrrolo[1,2-*a*]indol-3-one **326** and 9-cyanopyrrolo[1,2-*a*]indol-3-one **338** proceed smoothly in methanol to afford the 1,2-dihydro-1-phenylthio derivatives **383** and **384** in crude yields of 95% (Scheme 133). The adduct **383** was identified as the *anti* diastereomer on the basis of the three-bond coupling constant, 4.2 Hz.[48] These addition products were identified by comparison of the characteristic aliphatic proton resonances with **381** and by the molecular ion peaks in the mass spectra.

A crystal structure of 1,2-dihydro-1-phenylthio-pyrrolo[1,2-*a*]indol-3one **381**, shown in Figure 13 (bond length/angles given in Appendix, Table J), was obtained from a recrystallisation in toluene and confirms that the addition has occurred at the pyrrolo[1,2-*a*]indol-3one **2** 1-position. The C(1)-C(2) bond is significantly longer [1.544(4) Å] than that of **2** [1.333(2) Å] and comparable with the C(1)-C(2) bond

lengths of the hydrogenation product **347** and piperidine addition product **375** [1.536(2) Å and 1.5480(17) Å respectively].

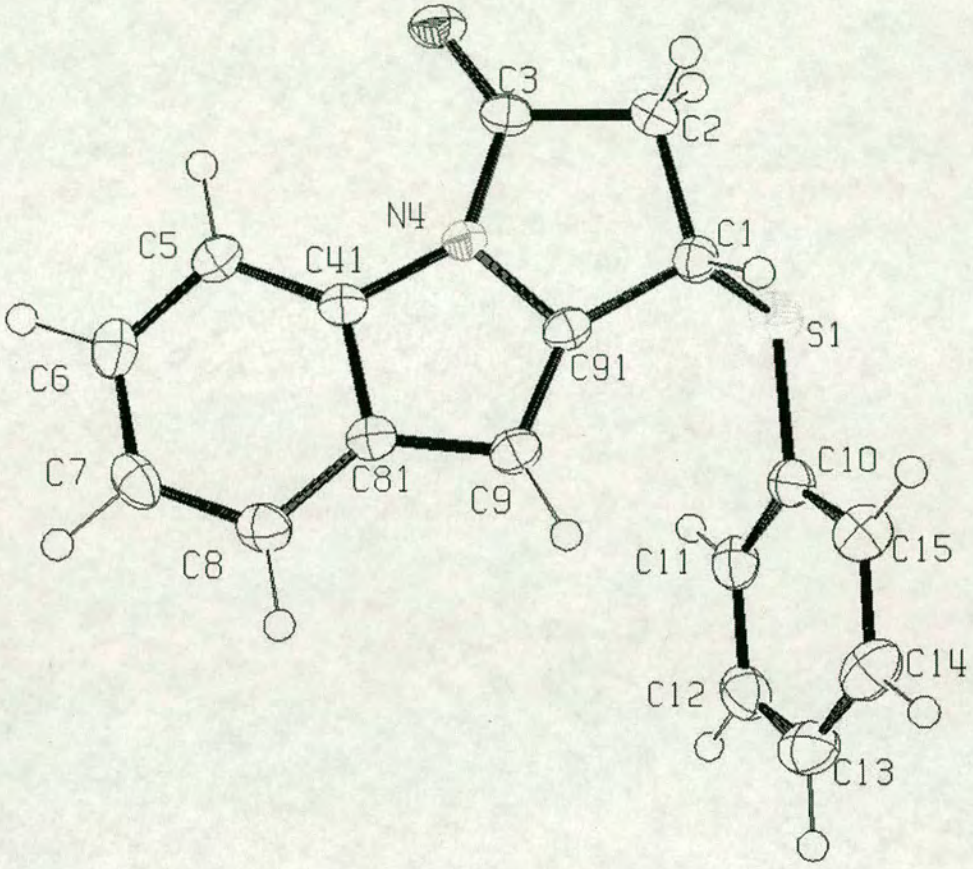
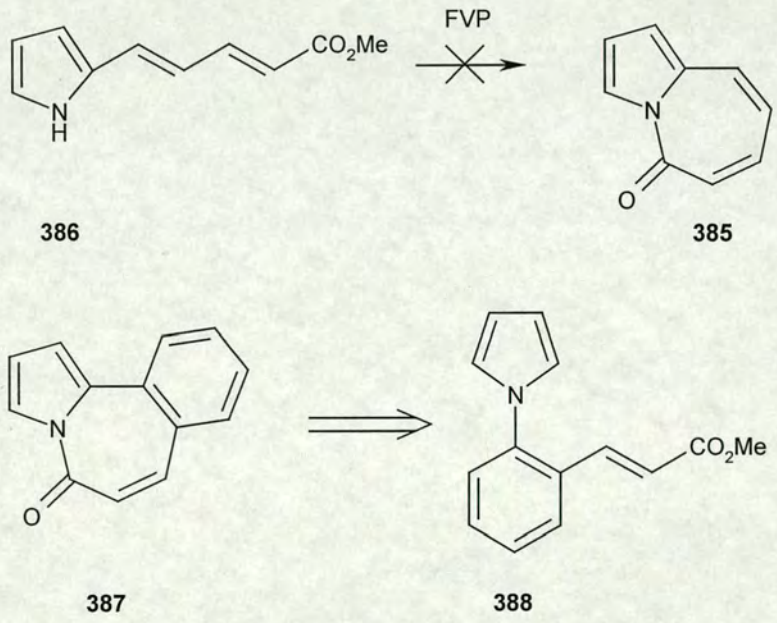


Figure 13 – crystal structure of 'Michael' adduct **381**

2.5 Flash vacuum pyrolysis of methyl 2-(pyrrol-1-yl)cinnamic acid methyl ester and novel synthesis of phenanthrene

2.5.1 Introduction

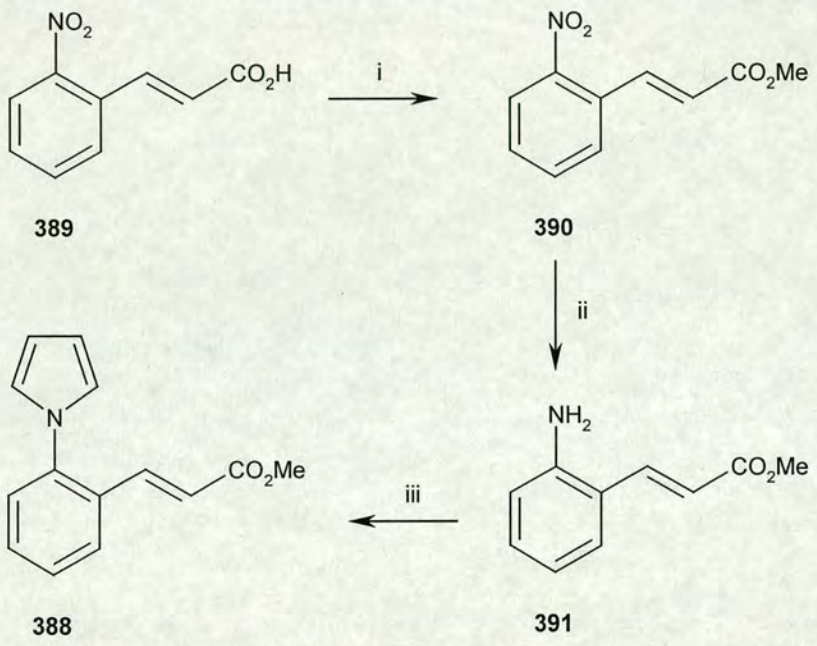
The versatility of elimination-cyclisation sequence in the formation of fused pyrrolone units (*e.g.* pyrrolizin-3-one **1**) is well established.[04] However, the formation of the azepinone **385** by pyrolysis of the vinylogous precursor **386** was not successful (Scheme 134).[04] This was assumed to be due to the rotational degrees of freedom in the diene at high pyrolysis temperatures. In order to investigate further azepinone formation by FVP it was reasoned that the incorporation of a fused benzene ring to the diene system would reduce the rotational degrees of freedom and therefore might favour cyclisation to the lactam **387**. The established viability of pyrrole *N*-benzoates and indole *N*-benzoates in lactam formation under FVP conditions lead to the selection of the cinnamic acid methyl ester **388** as a suitable precursor for pyrolysis.[45]



Scheme 134

2.5.2 Synthesis and flash vacuum pyrolysis of methyl 2-(pyrrol-1-yl)cinnamic acid methyl ester

Methyl 2-(pyrrol-1-yl)cinnamic acid methyl ester **388** was synthesised in three steps from 2-nitrocinnamic acid **389** by sequential formation of the ester **390**, selective reduction to the amino compound **391** by zinc dust in the presence of ammonium chloride and formation of the pyrrole ring by condensation with 2,5-dimethoxytetrahydrofuran in 18% overall yield (Scheme 135). The crude precursor **388** was purified by dry flash chromatography and characterised by standard methods with the proton NMR spectrum showing that the (*E*)-configuration of the alkene was maintained throughout (^3J 16.0 Hz).

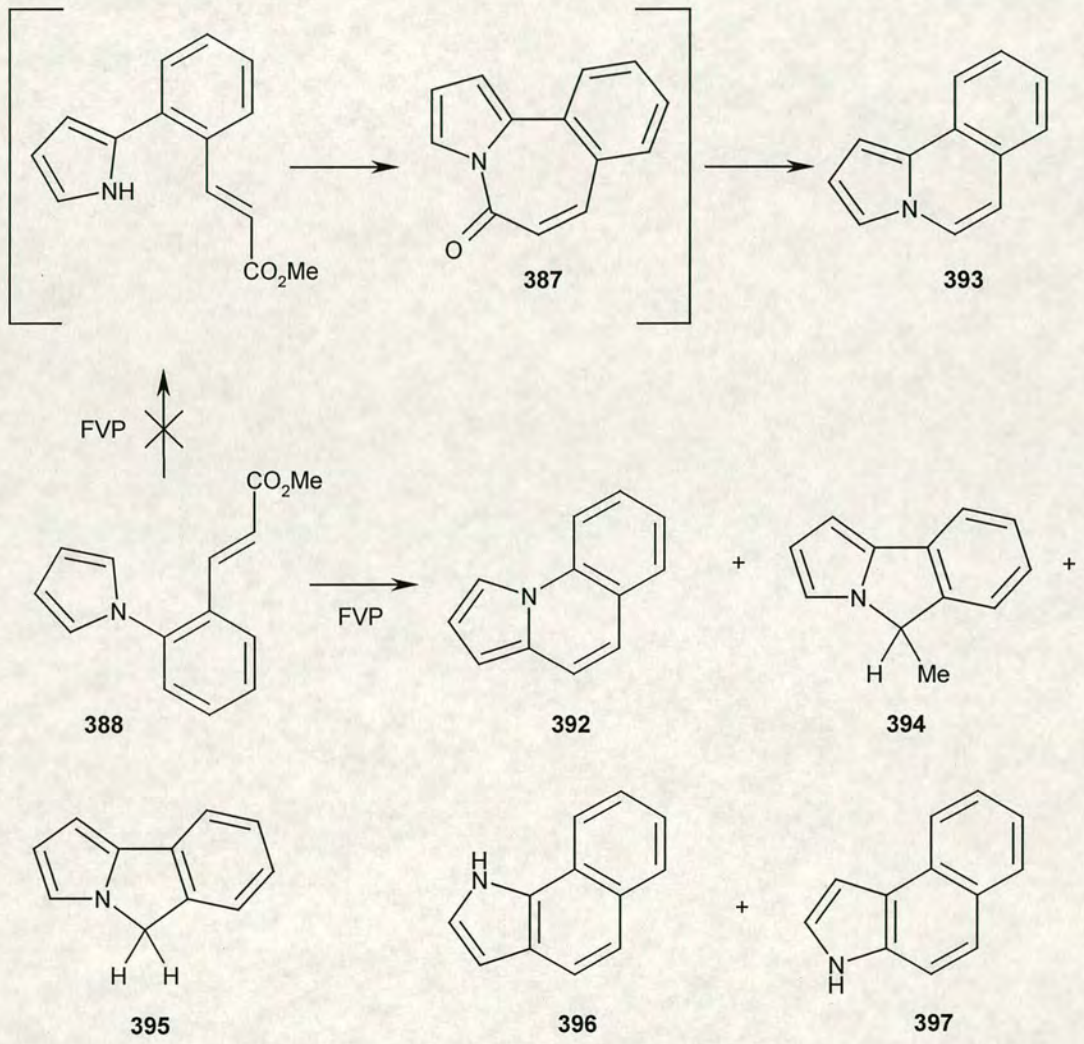


i) CH_3I, K_2CO_3, DMF; ii) MeOH/H_2O/NH_4Cl, zinc dust; iii) 2,5-dimethoxytetrahydrofuran, GAA

Scheme 135

The cinnamic acid methyl ester **388** was pyrolysed over a range of temperatures and the optimum temperature for full conversion of the precursor to products was found to be 850 °C. A large-scale pyrolysis of **388** (363 mg) was performed and T. L. C. analysis indicated that the pyrolysate contained four significant products which were isolated in low yield by dry flash chromatography (Scheme 136).

The first product to be eluted from the column was unambiguously identified as pyrrolo[1,2-*a*]quinoline **392** from the molecular ion at *m/z* 167 and comparison of the NMR spectra with literature data, which were found to be highly consistent.[99] The formation of the isomer pyrrolo[2,1-*a*]isoquinoline **393**, which might have been formed by loss of CO from the anticipated pyrroloazepinone **387**, was therefore excluded (Scheme 136).[100]

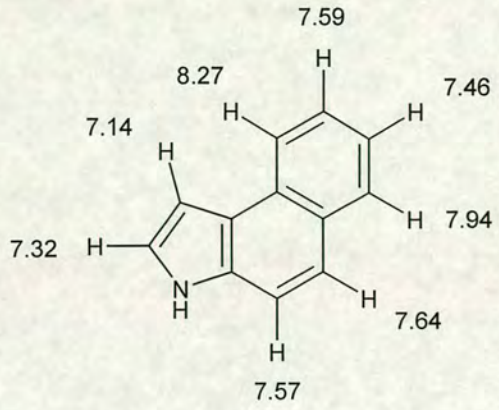


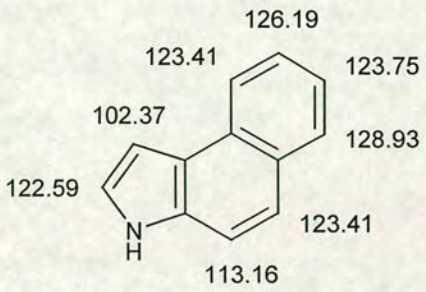
Scheme 136

The second product was obtained as the major component of an impure fraction. The molecular ion was found to be *m/z* 169 and the most significant features of its ^{1}H NMR spectrum were a mutually coupled doublet at δ_H 1.68 ppm and quartet δ_H 5.08

ppm in 3:1 integral ratio. The ^{13}C NMR spectrum showed one methyl group and eight CH resonances, one of which was in the aliphatic region at δ_C 56.9 ppm, apparently attached to a nitrogen atom. A NOESY experiment was performed that indicated that the methyl group was close in space to an aromatic proton as well as the aliphatic CH to which it is coupled. The 5-methylpyrrolo[2,1-*a*]isoindole structure **394** (R = Me) is consistent with these data (Scheme 136). Although **394** is not a known compound the methylene protons of the parent pyrrolo[2,1-*a*]isoindole **395** (R = H) resonate at δ_H 4.92 ppm which is very close to the chemical shift of the aliphatic proton in **394** (R = Me).[45,50] The remainder of the spectra are also very similar [**395** (R = H), aromatic protons δ_H 7.1-7.3 ppm, pyrrole-type protons δ_H 6.3-7.0 ppm;[45,50] **394** (R = Me), aromatic protons δ_H 7.2-7.5 ppm, pyrrole-type protons, δ_H 6.3-7.0 ppm].

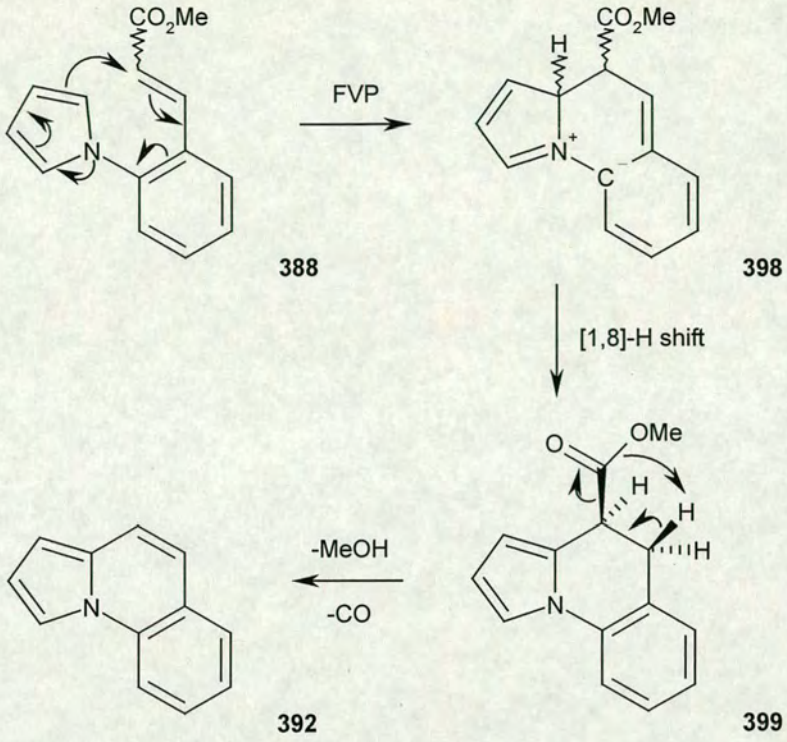
The final two products (14% in total) were closely related; although they co-eluted from the column, a pure sample of the component which was slightly more polar was obtained. Both products showed the presence of an NH signal in their ^1H NMR spectra, together with two other signals due to pyrrole-type protons and six signals in the aromatic region. The product which was not obtained in pure form, was unambiguously identified by comparison of its spectra with those reported for 1*H*-benz[*g*]indole **396**.[101] In particular the ^{13}C NMR spectra are closely comparable. The remaining isomer (molecular ion at *m/z* 167), was obtained in a pure state and identified as 3*H*-benz[*e*]indole **397** by the following NMR experiments. (The reported spectra of **397** are not sufficiently clear to allow unambiguous identification.[102]) NOESY (and COSY) correlations between the aromatic doublets at δ_H 7.57 ppm and δ_H 7.64 ppm define the 1,2-fusion of the naphthalene ring and a NOESY correlation between the pyrrole-type proton at δ_H 7.14 ppm and the aromatic doublet at δ_H 8.27 ppm defines the mode of fusion of the heterocycle (Scheme 136). Further NOESY correlations allow a complete assignment of the ^1H NMR spectrum and subsequent ^{13}C assignments were gained as a result of a $^1H/^{13}C$ HSQC experiment.





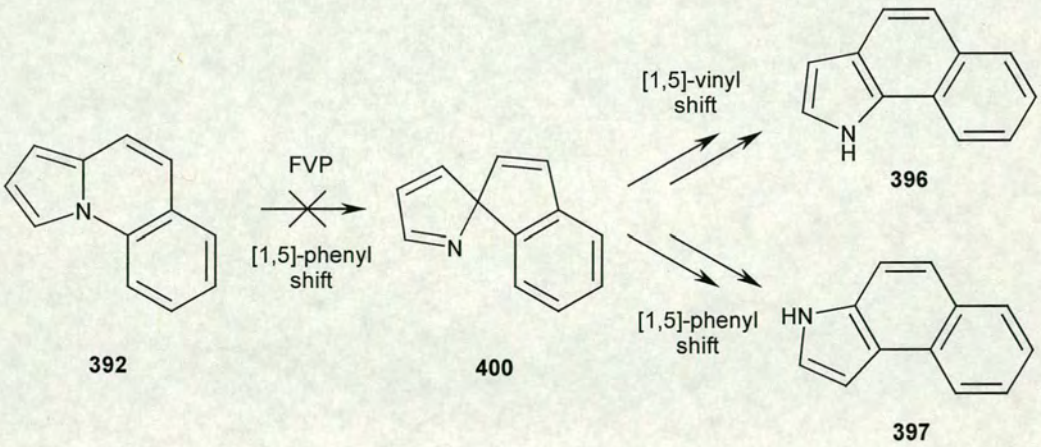
The results of the pyrolysis of the cinnamic acid methyl ester **388** show that the rearrangement-elimination-cyclisation cascade mechanism, previously seen in the formation of pyrrol-2-one units, does not occur in this case. Upon pyrolysis the precursor **388** has no clearly defined route to products and a number of competing pathways occur.

Pyrrolo[1,2-*a*]quinoline **392** is formed from **388** without skeletal rearrangement and therefore the cyclisation must involve loss of the entire ester function at an activation energy lower than that required to effect the [1,5]-aryl shift as in the cascade pathway. Such a cyclisation appears to be unprecedented. The most likely mechanism is *via* an initial electrocyclisation of **388** to generate the dipolar species **398** after which the aromaticity of the pyrrole and benzene rings is restored by a [1,8]-hydrogen shift to give the 4,5-dihydro compound **399**. The oxidative elimination of the ester group from **399** to afford **392** appears to be a novel process, which due to the competing pathways in the pyrolysis of **388** could not be studied directly. It was initially assumed that de-esterification occurred *via* a concerted elimination of methanol and carbon monoxide (Scheme 137).



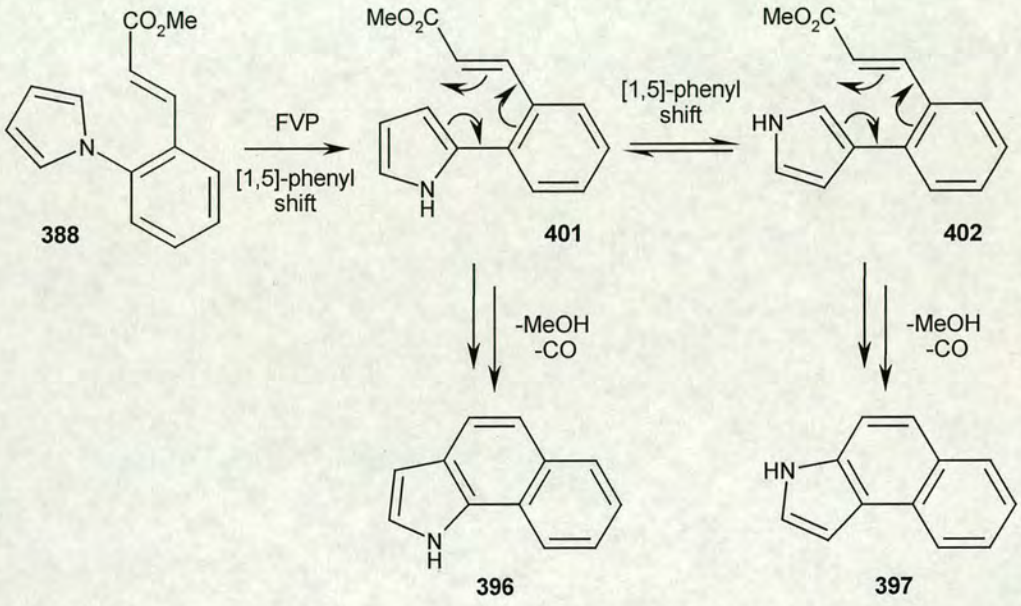
Scheme 137

1*H*-Benz[*g*]indole **396** and 3*H*-benz[*e*]indole **397** were initially thought to be formed *via* rearrangements of pyrrolo[1,2-*a*]quinoline **392** involving [1,5]-shifts and **400** as the key intermediate (Scheme 138).



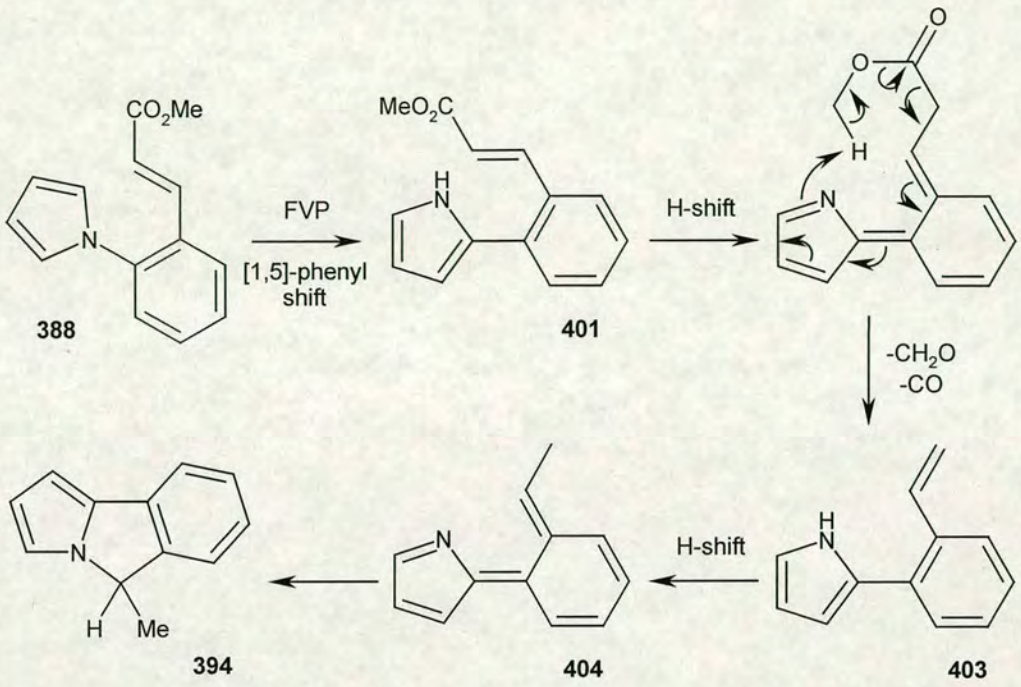
Scheme 138

However, control pyrolyses of **392** performed at temperatures of 850 °C and 950 °C failed to show any thermal rearrangement products in the proton NMR spectra. It is therefore probable that the products **396** and **397** are formed from the 2- and 3-arylpyrroles **401** and **402**, which are initially generated by a [1,5]-shift(s) of the aryl group, *via* the same oxidative elimination of the ester group as in the formation of **392** (Scheme 139). This suggests that once the [1,5]-aryl shift has occurred the elimination of methanol to generate the expected ketene intermediate required for lactam formation is disfavoured.



Scheme 139

The formation of the pyrroloisoindole **394** is unusual but a possible mechanism is shown in Scheme 140. It is proposed that the initial [1,5]-aryl shift is followed by a [1,9]-hydrogen shift leading to the intermediate **401** which can collapse to 2-(pyrrol-2-yl)styrene **403** by loss of CH_2=O and CO. A further [1,9]-hydrogen shift leads to the *o*-quinone dimethide **404** which is the precursor of the final product. It is again noteworthy that a route such as this apparently competes successfully with the expected ketene formation by methanol elimination from **401**.



Scheme 140

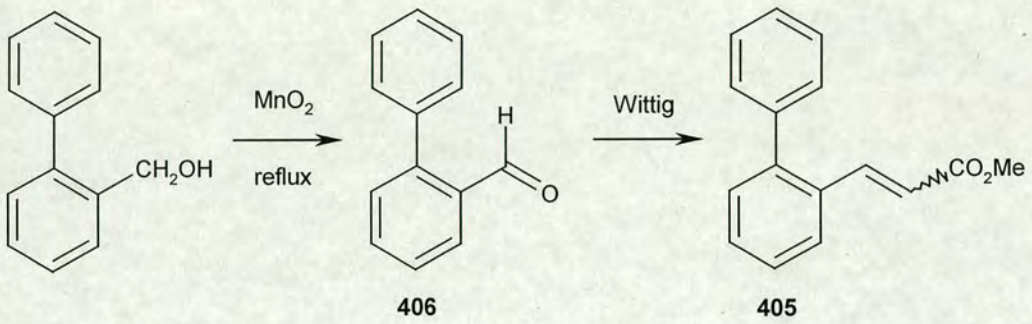
The results of the pyrolysis of methyl 2-(pyrrol-1-yl)cinnamic acid methyl ester **388** show that the sequence of [1,5]-aryl shift, *E/Z* isomerisation, thermal elimination of methanol and electrocyclisation to provide a fused azepinone system, cannot compete with alternative thermal processes. Product **392** is formed from **388** even prior to the expected sigmatropic shift of the *N*-aryl group and the other major products **394**, **396** and **397** are obtained after sigmatropic shift, but are formed in preference to the azepinone **387** or its decomposition products (*e.g.* **393**). It is therefore concluded that the methanol elimination step (required for the formation of **387** *via* a eight- or nine-membered transition state) is not feasible geometrically, even though the formation of five-membered rings (*via* a six- or seven-membered transition state) is highly efficient.

2.5.3 Synthesis of phenanthrene

Although the pyrolysis of methyl 2-(pyrrol-1-yl)cinnamate **387** was complicated by competing pathways, three of the four identified products appeared to have been

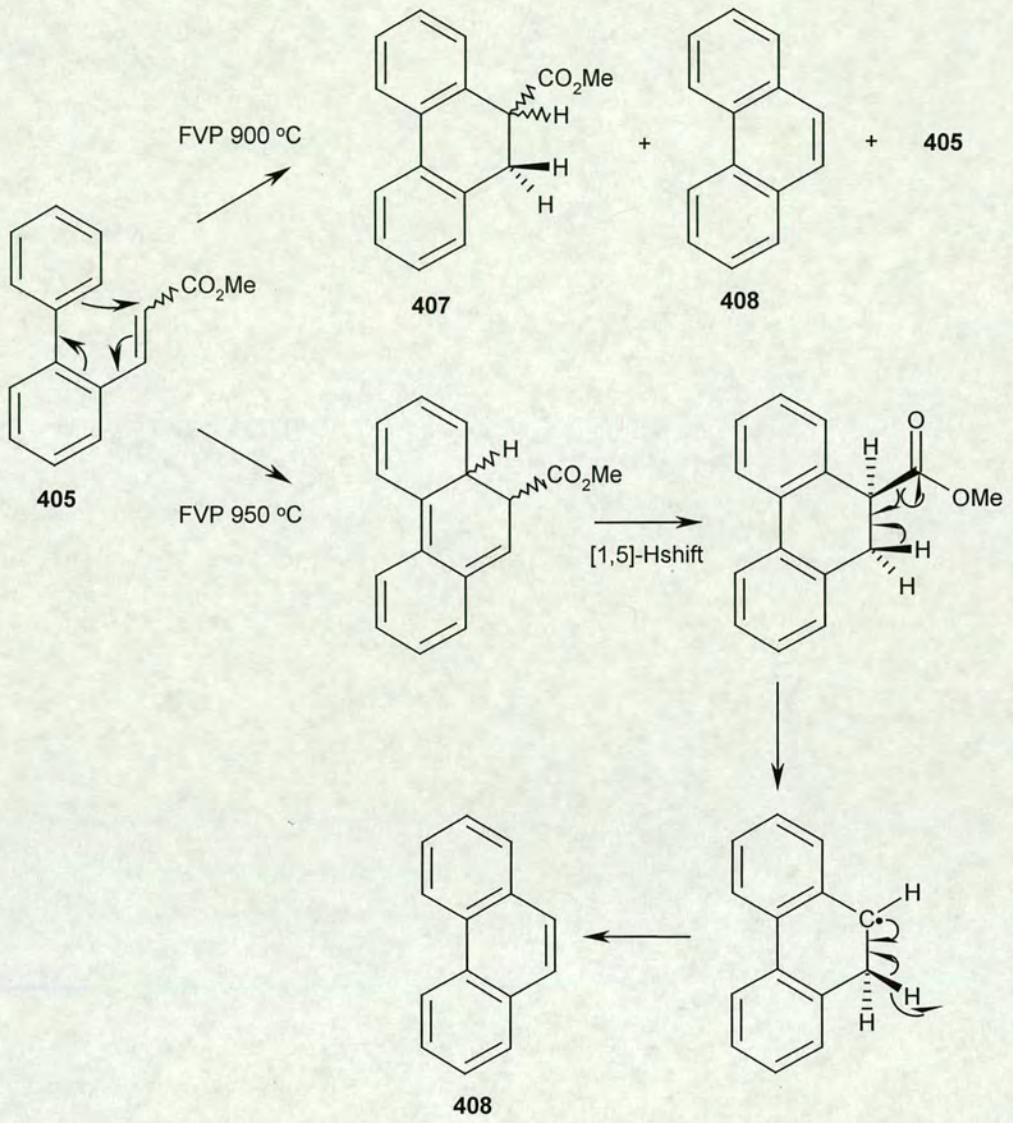
generated *via* oxidative elimination of the ester group as the key aromatisation step after an electrocyclisation process. The synthetic viability of the newly recognised process was evaluated by pyrolysis of the structurally more simple biphenyl acrylic acid methyl ester **405**.

The precursor, 3-(biphenyl-2-yl)-acrylic acid methyl ester **405**, was synthesised from biphenyl 2-methanol by oxidation with manganese dioxide to give biphenyl 2-carbaldehyde **406** followed by a Wittig reaction with methyl (triphenylphosphoranylidene)acetate to afford **405** (Scheme 141). Purification was readily achieved by dry flash chromatography to give isolated **405** in 75% overall yield which was identified by comparison of the NMR spectra with literature data.[103]



Scheme 141

Pyrolysis of the precursor **405** was performed at 850 °C, 900 °C and 950 °C. At the lower temperatures the pyrolysates were found to contain recovered substrate **405** and methyl 9,10-dihydrophenanthrene-9-carboxylate **407**. However, FVP of **405** was found to proceed smoothly at 950 °C to give exclusively phenanthrene **408** as a white solid in 95% yield, which was identified by comparison of NMR spectra and the mass spectrum with authentic data (Scheme 142).[104]



Scheme 142

The mechanism of the oxidative elimination is also the subject of ongoing research.[106] It has been found that the elimination does not occur *via* the concerted loss of methanol and carbon monoxide since no methanol could be trapped in control pyrolyses. The pyrolytic behaviour of model compounds bearing structural features related to those of **405** was examined and form these results it was concluded that the most likely mechanism for the oxidative elimination involves radical cleavage of the ester group (Scheme 142). The position of the ester group at a benzylic site is essential for the process to occur.[105]

This result suggests that cyclisation *via* the novel de-esterification potentially has use as a general synthetic method. Further applications in the synthesis of polycyclic ring systems have shown the methodology to be compatible with 3-ring and 4-ring fused systems, with or without heteroatoms, and yields are uniformly high.[105]

EXPERIMENTAL

3.1 Abbreviations

FVP	flash vacuum pyrolysis
T_i	inlet temperature
T_f	furnace temperature
P_{range}	pressure range (Torr)
t	pyrolysis duration
$CDCl_3$	deuteriated chloroform
DMSO	dimethyl sulfoxide
DCM	dichloromethane
DMF	*N*,*N*-dimethylformamide
GAA	glacial acetic acid
DBU	1,8-diazabicyclo[5,4,0]undec-7-ene
NBS	*N*-bromosuccinimide
AIBN	α,α'-azobisisobutyronitrile
LDA	lithium diisopropylamide
DMA	*N*,*N*-dimethylacetamide
DMAP	dimethylaminopyridine
DIPEA	diisopropylethylamine
TEAC	tetraethylammonium chloride
TBAC	tetrabutylammonium chloride
TBAF	tetrabutylammonium fluoride
TMSCl	trimethylsilyl chloride
Triton B	benzyltrimethylammonium hydroxide
$MgSO_4$	anhydrous magnesium sulfate
NMR	nuclear magnetic resonance
δ_H, δ_C	chemical shift
ppm	parts per million
s	singlet
d	doublet
t	triplet
q	quartet (^1H)

quin	quintet
br	broad
quat	quaternary (^{13}C)
m	multiplet
J	coupling constant
Hz	Hertz
IR	infra-red
ν	wavenumber
m/z	mass to charge ratio
M^+	mass of molecular ion
e.i.	electron impact
FAB	fast atom bombardment
mp	melting point
bp	boiling point
t.l.c.	thin layer chromatography
s	seconds
min	minutes
h	hours
g	grams
mg	milligrams
mol	moles
mmol	millimoles
M	molarity
atm	atmospheres
PSI	pounds per square inch

3.2 Instrumentation and general techniques

3.2.1 Reagents and solvents

All reagents and solvents are commercially available and were used without further purification. Where necessary, diethyl ether and tetrahydrofuran were dried over sodium wire and distilled prior to use. All other dried solvents were obtained by storing over molecular sieves (4A).

3.2.2 Nuclear magnetic resonance spectroscopy

^{1}H NMR spectra were recorded on Bruker AC200 (200 MHz), Bruker ARX250 (250 MHz), Bruker DPX360 (360 MHz), and Varian Gemini 200 (200 MHz) spectrometers. ^{13}C NMR spectra were recorded on Bruker AC200 (50 MHz) and Bruker AC250 (63 MHz) spectrometers. The Bruker spectrometers were operated by Mr. J. R. A. Millar and Mr. W. G. Kerr.

All spectra were recorded in [^{2}H] chloroform unless otherwise stated and chemical shifts for both ^{1}H and ^{13}C spectra are in ppm relative to trimethylsilane. ^{13}C NMR signals refer to CH peaks unless otherwise stated. Coupling constants are quoted in Hertz (Hz).

3.2.3 Mass spectroscopy

All spectra were recorded using electron impact ionisation unless otherwise stated. Low resolution electron impact spectra were recorded on a Kratos Profile spectrometer operated by Mr. H. G. McKenzie. High resolution and FAB mass spectra were recorded on a Kratos MS50 TC spectrometer operated by Mr. A. T. Taylor.

3.2.4 Infra-red spectroscopy

IR spectra were obtained as nujol mulls or liquid films on a Perkin Elmer Paragon 1000 FT-IR spectrometer. All spectral data are quoted in wavenumbers (cm^{-1}).

3.2.5 UV/Visible spectroscopy

UV/visible spectra were recorded in chloroform on a Perkin Elmer 900 Lambda spectrometer. All spectral data are quoted in nanometres (nm).

3.2.6 Elemental analysis

All microanalyses were obtained on an Exeter Analytical CE 440 CHN elemental analyser by Mrs. L. J. Eades and Mrs. S. Djurdjevic. Many compounds synthesised during the course of this research are unstable and purification is not always possible. In these cases accurate mass is recorded rather than elemental analysis.

3.2.7 Structural determination

Crystal structures were obtained and solved by Dr. R. O. Gould and Dr. S. Parsons and their co-workers on a Stoe STADI-4 four circle diffractometer with graphite monochronator.

3.2.8 Chromatography

Thin layer chromatography was performed on pre-coated aluminium sheets (0.2 mm, Merck, grade 60) impregnated with an UV fluorescent indicator.

Dry flash chromatography was performed on silica gel (Merck, grade 60, 230-400 mesh, 60Å) by the method of L. M. Harwood.[106] A column was packed to a depth of approximately 2.5 cm under suction at a water pump and the crude materials, pre-absorbed onto silica, then loaded on top of the column. Fractions were drawn from the column individually, allowing the column to run dry before the next fraction was added. Elution systems were most commonly composed of ethyl acetate or DCM in *n*-hexane although in some cases 3-component systems (generally ethyl acetate and DCM in *n*-hexane) were required to achieve suitable separation. Occasionally an elution gradient was used for enhanced separation of column products.

3.2.9 Flash vacuum pyrolysis

The apparatus used for flash vacuum pyrolysis is illustrated in Figure 14. It is based on the design by W. D. Crow of the Australian National University.

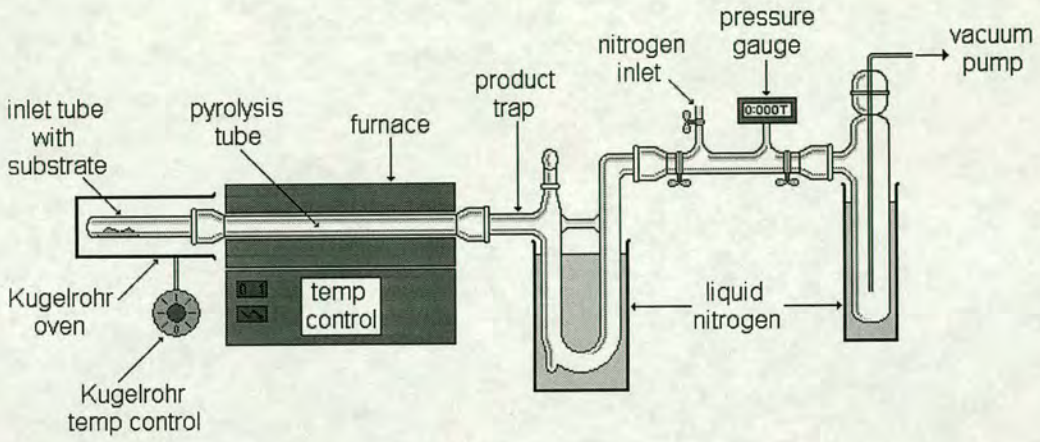


Figure 14 - Flash vacuum pyrolysis apparatus

The system is evacuated by use of an Edwards Model ED100 high capacity oil pump to maintain the pressure in the region of 0.030 Torr. A glass Büchi oven is used to heat the inlet tube in which the substrate is placed until it volatilises. The gaseous substrate passes through a silica tube (30 x 2.5 cm) heated by a Carbolite electronically controlled laboratory tube furnace (model number MTF 12/38/250). The estimated contact time in the hot zone is of the order of ten milliseconds and the gaseous phase of the substrate under vacuum ensures that intramolecular reactions are strongly favoured. The products are captured at the exit of the furnace in a U-shaped trap cooled in liquid nitrogen. Upon completion of the reaction the pump is isolated and the trap allowed to warm to room temperature under a dry nitrogen atmosphere.

"Small scale" pyrolyses are those involving 20-50 mg of substrate. The entire pyrolysate is dissolved into a suitable solvent (usually $CDCl_3$) for examination by NMR spectroscopy of the crude reaction products. "Large scale" pyrolyses are those involving 0.1 g or more of substrate.

In some cases a pyrolysate may be thermally unstable under the standard FVP conditions described above. In the event of such a pyrolysate being formed, the U-

shaped trap can be exchanged for a dry ice/acetone 'cold-finger' trap, as illustrated in Figure 15, allowing unstable products to collect on the 'cold-finger' surface and be kept cold for the duration of a pyrolysis. Products can then be removed from the trap, under a dry nitrogen atmosphere, into a suitable solvent for immediate NMR spectroscopic analysis.

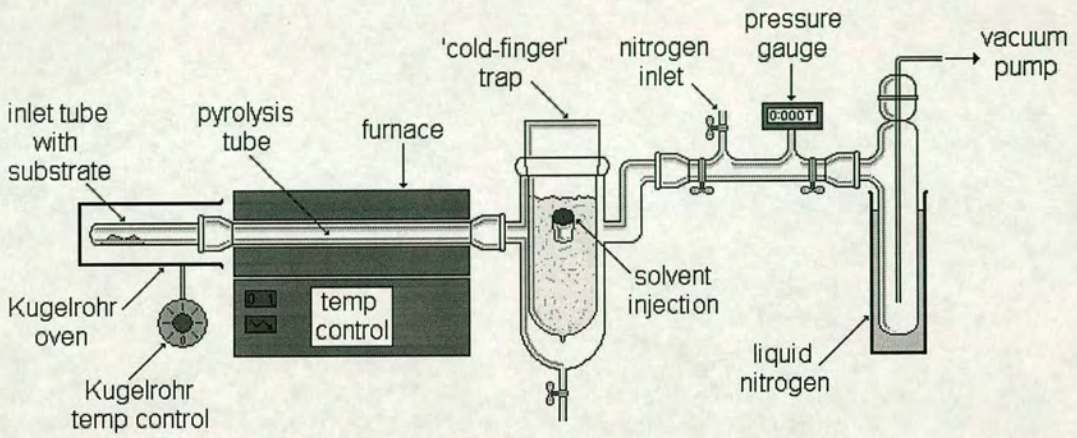


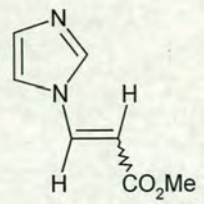
Figure 15 - Flash vacuum pyrolysis apparatus with 'cold-finger' trap

Controllable parameters are quoted as follows: inlet temperature (T_i), furnace temperature (T_f), pressure range (P_{range}) and total pyrolysis time (t).

3.3 Synthesis of pyrroloimidazol-5-ones

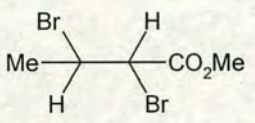
3.3.1 Pyrroloimidazol-5-one precursors

3-(2*H*-Imidazol-1-yl)-acrylic acid methyl ester 254.



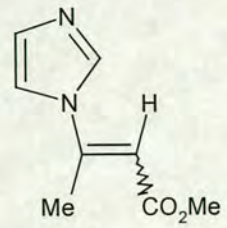
A solution of propynoic acid methyl ester (4.20 g, 0.05 mol) and imidazole (3.63 g, 0.05 mol) in toluene (15 cm^3) was heated under reflux for 2 h. Cooling resulted in the crystallisation of the *trans*-isomer of the product **254a**. The product was filtered and recrystallised from a minimum volume of toluene. The filtrate was concentrated under reduced pressure to low volume and crystallisation of the *cis*-isomer followed. This product was filtered then dissolved in ethyl acetate and hexane added to precipitate unreacted imidazole that was removed by filtration. The filtrate was then concentrated under reduced pressure to give the *cis*-isomer **254b** which was recrystallised from a minimum volume of toluene (6.42 g, 82%; 3.11 g *trans*, 3.31 g, *cis*),[107] mp_{trans} 117-119 °C [lit.,[107] 121-122 °C], mp_{cis} 46-48 °C [no lit. mp reported]; δ_{Htrans} 7.86 (1H, d, ^3J 14.3), 7.74 (1H, s), 7.19 (1H, s), 7.10 (1H, s), 6.01 (1H, d, ^3J 14.3), 3.74 (3H, s); δ_{Hcis} 8.02 (1H, s), 7.79 (1H, s), 7.02 (1H, s), 6.85 (1H, d, ^3J 10.6), 5.44 (1H, d, ^3J 10.6) and 3.69 (3H, s); δ_{Ctrans} 166.10 (quat), 137.67, 136.38, 131.55, 115.90, 106.24 and 51.70 (CH_3); δ_{Ccis} 166.86 (quat), 136.07 (2CH), 130.17, 115.53, 106.21 and 52.14 (CH_3).

2,3-Dibromobutyric acid methyl ester 251.



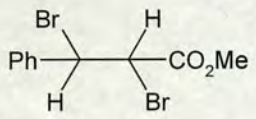
Methyl *trans*-crotonate (2.02 g, 20 mmol) was dissolved in dichloromethane (25 cm^3) with stirring. The solution was cooled in an ice-bath and a solution of bromine (3.28 g, 20 mmol) in dichloromethane (25 cm^3) was added dropwise over 1 h. The solution was left to stir for a further 40 min until completely decolourised. Dichloromethane was removed by rotary evaporator to give the product (4.98 g, 94%) which was sufficiently pure for further reaction;[107] δ_H 4.32-4.48 (2H, m), 3.79 (3H, s) and 1.86 (3H, d, ^3J 6.2).

3-(2*H*-Imidazol-1-yl)-but-2-enoic acid methyl ester 250.



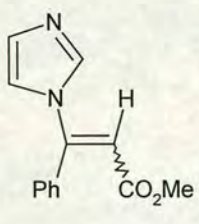
2,3-Dibromobutyric acid methyl ester (4.98 g, 19 mmol) was added to a solution of imidazole (1.85 g, 27 mmol) and triethylamine (5.0 g, 50 mmol) in toluene (140 cm^3) and heated under reflux overnight. Water (50 cm^3) was added to the cooled solution to dissolve the solids present. The mixture was extracted with dichloromethane (3 × 150 cm^3), washed with water (100 cm^3) and dried over magnesium sulfate. The crude product was purified by dry flash chromatography on silica (50% ethyl acetate in hexane) to give both isomers of 3-(2*H*-imidazol-1-yl)-but-2-enoic acid methyl ester **250** as a co-eluted mixture in a 80:20 ratio in favour of the *E*-isomer (1.45 g, 47%);[107] mp 86-88 °C [lit.,[107] 88-88.5 °C]; δ_{Htrans} 7.80 (1H, s), 7.18 (1H, d, ^nJ 1.2), 7.03 (1H, d, ^nJ 1.2), 5.94 (1H, s), 3.67 (3H, s) and 2.62 (3H, s); δ_{Hcis} 7.65 (1H, s), 7.38 (1H,s), 6.83 (1H, s), 5.69 (1H, s), 3.59 (3H, s) and 2.22 (3H, s); *m/z* 166 (M^+, 100%), 135 (68), 107 (60), 95 (70) and 80 (72).

2,3-Dibromo-3-phenylpropionic acid methyl ester 252.



Methyl *trans*-cinnamate (1.68 g, 10 mmol) was dissolved in dichloromethane (25 cm^3) with stirring. The solution was cooled in an ice-bath and a solution of bromine (1.78 g, 11 mmol) in dichloromethane (25 cm^3) was added dropwise over 1 h. The solution was left to stir for a further 80 min until completely decolourised. Dichloromethane was removed by rotary evaporator to give the product (3.19 g, 95%) which was sufficiently pure for further reaction;[45] δ_H 7.27-7.35 (5H, m), 5.27 (1H, d, ^3J 11.8), 4.77 (1H, d, ^3J 11.8) and 3.82 (3H, s).

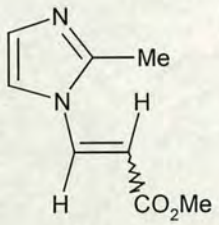
3-(2*H*-Imidazol-1-yl)-3-phenylacrylic acid methyl ester 246.



2,3-Dibromo-3-phenyl propionic acid methyl ester (3.19 g, 10 mmol) was added to a solution of imidazole (1.00 g, 15 mmol) and triethylamine (5.0 g, 50 mmol) in toluene (100 cm^3) and heated under reflux overnight. Water (60 cm^3) was added to the cooled reaction to dissolve the solids present. The solution was

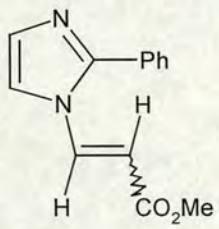
extracted with dichloromethane (3 × 50 cm^3), washed with water (60 cm^3) and dried over magnesium sulfate. The crude product was purified by dry flash chromatography on silica (50% ethyl acetate in hexane) to give a 17:83 isomer mixture of 3-(2*H*-imidazol-1-yl)-3-phenyl acrylic acid methyl ester **246** (1.74 g, 78%)[45,107] mp 102-103 °C (lit.,[107] 102-103 °C) which was not further analysed; δ_{Hmajor} 7.51 (1H, s), 7.46-7.14 (5H, m), 7.06 (1H, d, ^4J 1.1), 6.84 (1H, d, ^4J 1.1), 6.16 (1H, s) and 3.59 (3H, s); δ_{Hminor} 7.00 (2H, dd, ^3J 6.6, ^4J 1.1), 6.06 (1H, s) and 3.52 (3H, s), other signals overlapping.

3-(2-Methylimidazol-1-yl)-acrylic acid methyl ester 255.



2-Methylimidazole (1.23 g, 15 mmol) and propynoic acid methyl ester (1.26 g, 15 mmol) were added to toluene (15 cm^3) and heated under reflux for 2 h during which time the reaction darkened to deep yellow. Removal of the solvent under reduced pressure afforded crystallisation of the product which was filtered and recrystallised from toluene to give *trans*-3-(2-methyl-imidzol-1-yl)-acrylic acid methyl ester **255** only (1.36 g, 55%) mp 92-93 °C [lit.,[108] 91-92 °C] δ_H 7.84 (1H, d, ^3J 14.1), 7.15 (1H, s), 6.97 (1H, s), 5.93 (1H, d, ^3J 14.1), 3.88 (3H, s) and 2.50 (3H,s); *m/z* 166 (M^+, 100), 135 (82), 107 (81), 81 (28) and 67 (38).

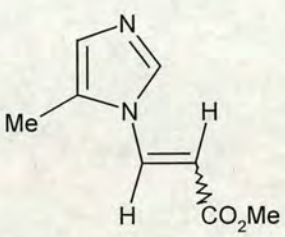
3-(2-Phenylimidazol-1-yl)-acrylic acid methyl ester 256.

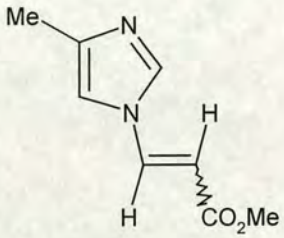


A solution of 2-phenylimidazole (0.43 g, 3 mmol) and propynoic acid methyl ester (0.25 g, 3 mmol) in toluene was heated under reflux for 4 h after which the solvent was removed under reduced pressure and the crude product purified by Kugelrohr distillation to give *3-(2-phenylimidazol-1-yl)-acrylic acid methyl ester* **256** (0.42 g, 61%) as a 34:66 mixture of *cis* and *trans* isomers respectively, bp 179 °C (3.8 mbar) (Found: C, 68.4; H, 5.4; N, 12.05. $C_{13}H_{12}N_2O_2$ requires C, 68.4; H, 5.25; N, 12.3); (Found: M^+ 228.0891. $C_{13}H_{12}N_2O_2$ requires *M* 228.0898); δ_{Htrans} 8.02 (1H, d, ^3J 14.1), 7.59-7.52 (5H, m), 7.40 (1H, s), 7.18 (1H, s), 6.09 (1H, d, ^3J 14.1) and 3.81 (3H, s); δ_{Hcis} 7.99 (1H, s), 7.59-7.39 (6H,

m), 7.20 (1H, s), 6.93 (1H, d, ^3J 10.3), 5.61 (1H, d, ^3J 10.3) and 3.82 (3H, s); δ_{Ctrans} 166.92 (quat), 149.95 (quat), 137.79, 131.42, 130.26, 130.03 (2CH), 129.37 (2CH), 117.01, 107.50 and 52.39 (CH_3) one quaternary overlapping; δ_{Ccis} 165.07 (quat), 134.85, 129.96 (2CH), 129.44 (2CH), 129.11 (2CH), 122.35, 107.82, 52.26 (CH_3), two quaternaries overlapping; *m/z* 228 (M^+, 85), 197 (48), 169 (100), 157 (49) and 128 (36).

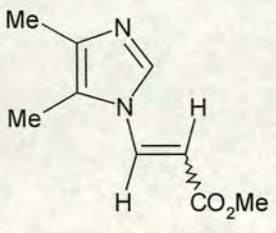
Reaction of 4(5)-methylimidazole with propynoic acid methyl ester.





4-Methylimidazole (0.41 g, 5 mmol) and propynoic acid methyl ester (0.42 g, 5 mmol) were added to toluene (15 cm^3) and heated under reflux for 2 h during which time the reaction darkened to deep yellow. The solvent was removed under reduced pressure to afford a deep yellow crude liquid that was distilled [136 °C (5.0 mbar)] yielding a yellow oil (0.67 g, 80%). A proton NMR spectrum showed four characteristic doublets pertaining to an α-methine proton of a propenoate carbon-carbon double bond in each case and hence indicating that the oil contained *trans* and *cis* isomers of both *3-(4-methylimidazol-1-yl)-acrylic acid methyl ester* **260** and *3-(5-methylimidazol-1-yl)-acrylic acid methyl ester* **261**. Separation of the 4-methyl and 5-methyl products could not be achieved by distillation or by dry flash chromatography (very similar R_f values in all eluents).

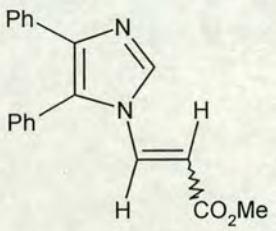
3-(4,5-Dimethylimidazol-1-yl)-acrylic acid methyl ester 257.



Propynoic acid methyl ester (0.27 g, 3.2 mmol) was added to a solution of 4,5-dimethylimidazole (0.26 g, 2.7 mmol) in toluene (25 cm^3) and the solution heated under reflux, with stirring, for 30 min. Crystallisation resulted from removal of the solvent under reduced pressure after which the crude product was filtered then recrystallised from the minimum volume of toluene (8 cm^3) to give *3-(4,5-dimethyl-imidazol-1-yl)-acrylic acid methyl ester* **257**

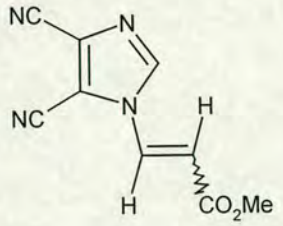
(0.39 g, 79%) as a 67:33 *E:Z* isomer mixture, mp 172-174 °C; (Found: M^+ 180.0890. $C_9H_{12}N_2O_2$ requires *M* 180.0899); δ_{Htrans} 7.70 (1H, s), 7.68 (1H, d, ^3J 14.3), 6.00 (1H, d, ^3J 14.3), 3.73 (3H, s), 2.16 (3H, s) and 2.10 (3H, s); δ_{Hcis} 8.53 (1H, s), 6.79 (1H, d, ^3J 10.5), 5.67 (1H, d, ^3J 10.5), 3.66 (3H, s), 2.16 (3H, s) and 2.10 (3H, s); δ_{Ctrans} 167.07 (quat), 136.34 (quat), 136.03, 133.76, 122.62 (quat), 105.77, 52.16 (CH_3), 12.74 (CH_3) and 9.08 (CH_3); δ_{Ccis} 165.20 (quat), 137.75, 134.38 (quat), 131.85, 122.34, 106.77, 52.10 (CH_3), 12.74 (CH_3) and 9.08 (CH_3); *m/z* 180 (M^+, 100%), 179 (17), 165 (14), 164 (15), 149 (27), 121 (38), 93 (22), 80 (23) and 70 (45).

3-(4,5-Diphenylimidazol-1-yl)-acrylic acid methyl ester 258.



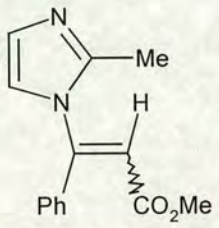
Propynoic acid methyl ester (0.21 g, 2.5 mmol) was added to a solution of 4,5-diphenylimidazole (0.55 g, 2.5 mmol) in chloroform (25 cm^3) in the presence of triethylamine (1 cm^3) and the solution was heated under reflux, with stirring, for 72 h. The solvent was removed under reduced pressure and the crude product was purified by dry flash chromatography (10-40% ethyl acetate in hexane as eluent) to give *3-(4,5-diphenylimidazol-1-yl)-acrylic acid methyl ester* **258** (0.45 g, 59%) as a 88:12 *E/Z* isomer mixture, mp 208-210 °C (from toluene) (Found: C, 74.90; H, 5.25; N, 8.95. $C_{19}H_{16}N_2O_2$ requires C, 75.00; H, 5.25; N, 9.20); (Found: M^+ 304.1211. $C_{19}H_{16}N_2O_2$ requires *M* 304.1211); δ_{Htrans} 8.06 (1H, s), 7.54 (1H, d, ^3J 14.5), 7.51-7.42 (5H, m), 7.43-7.29 (2H, m) 7.24-7.16 (3H, m) 6.07 (1H, d, ^3J 14.5) and 3.70 (3H, s); δ_{Hcis} 8.73 (1H, s), 6.53 (1H, d, ^3J 10.3), 5.54 (1H, d, ^3J 10.3) and 3.75 (3H, s) with other signals overlapping; δ_{Ctrans} 166.80 (quat), 140.30 (quat), 136.24, 134.95, 133.64 (quat), 131.51 (2CH), 129.97, 129.85 (2CH), 129.10 (quat), 128.73 (2CH), 128.31 (quat), 127.65, 127.35 (2CH), 107.56 and 52.38 (CH_3); δ_{Ccis} 139.40, 132.50 and 108.18 (all other signals were indistinguishable); *m/z* 304 (M^+, 93%), 273 (14), 245 (100), 219 (97), 190 (32), 165 (85), 142 (30), 115 (49) and 89 (54).

3-(4,5-Dicyanoimidazol-1-yl)-acrylic acid methyl ester 259.



Propynoic acid methyl ester (0.29 g, 3.5 mmol) was added to a solution of 4,5-dicyanoimidazole (0.41 g, 3.5 mmol) in chloroform (25 cm^3) in the presence of triethylamine (1 cm^3) and the solution was heated under reflux, with stirring, for 72 h. The crude product was purified by dry flash chromatography (10-20% ethyl acetate in hexane as eluent) to give *3-(4,5-dicyanoimidazol-1-yl)-acrylic acid methyl ester* **259** as a 90:10 *E/Z* isomer mixture (0.04 g total, 6%), mp 140-142 °C (Found: M^+ 202.0494. $C_9H_6N_4O_2$ requires *M* 202.0491); δ_{Htrans} ([$^2H_6$]acetone) 8.76 (1H, s), 8.08 (1H, d, ^3J 14.4), 6.83 (1H, d, ^3J 14.4) and 3.83 (3H, s); δ_{Hcis} 7.90 (1H, d, ^3J 12.1), 5.67 (1H, d, ^3J 12.1) and 3.69 (3H, s) (imidazole singlet indistinguishable); δ_{Ctrans} 163.78 (quat), 140.91, 133.06, 122.98 (quat), 112.78, 110.86 (CN), 110.57 (CN), 107.12 and 50.92; *m/z* 202 (M^+, 8%), 171 (17), 156 (53), 155 (98), 154 (100), 153 (99), 152 (76), 146 (36), 118 (53) and 113 (72).

3-(2-Methylimidazol-1-yl)-3-phenylacrylic acid methyl ester 253.



A solution of 2-methylimidazole (0.68 g, 8.2 mmol) and 2,3-dibromo-3-phenylpropionic acid methyl ester **252** (1.34 g, 4.1 mmol) in toluene (35 ml) in the presence of triethylamine (5 cm^3) was heated under reflux overnight. The solvent was removed under reduced pressure and the crude product purified by dry flash chromatography (40% ethyl acetate in hexane as eluent) followed by Kugelrohr distillation to give *3-(2-methylimidazol-1-yl)-3-phenylacrylic acid methyl ester* **253** as a 86:14 isomer mixture (0.70 g, 70%), bp 168 °C (3.0 Torr) (Found: M^+ 242.1052. $C_{14}H_{14}N_2O_2$ requires *M* 242.1053). δ_{Hmajor} 7.42-7.27 (3H, m), 7.17-7.13 (2H, m), 6.98 (1H, d, ^3J 1.5), 6.73 (1H, d, ^3J 1.5), 6.47 (1H, s), 3.58 (3H, s) and 2.09 (3H, s); δ_{Hminor} 6.86 (1H, d, ^3J 1.5), 6.77 (1H, d, ^3J 1.5), 5.95 (1H, s) and 2.04 (3H, s) (other signals indistinguishable); δ_{Cmajor} 163.70 (quat), 146.91 (quat), 145.14 (quat), 134.73 (quat), 131.10, 129.01 (2CH), 127.59, 126.38 (2CH), 119.96, 114.67, 51.61 (CH_3) and 12.70 (CH_3); δ_{Cminor} 165.06 (quat), 149.05 (quat), 145.36 (quat), 133.40 (quat), 130.46, 128.01, 120.59, 113.80, 51.47 (CH_3) and 14.31 (CH_3) (other signals

indistinguishable); *m/z* 242 (M^+, 90%), 211 (59), 183 (88), 161 (47), 129 (36), 115 (60), 102 (76) and 56 (100).

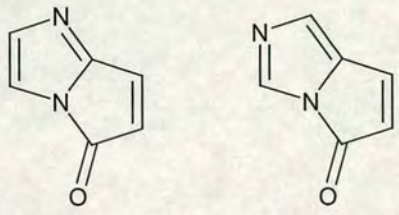
3.3.2 Synthesis of pyrroloimidazol-5-ones by flash vacuum pyrolysis

Pyrolysate characterisation

In the following cases where two products have been generated by pyrolysis full characterisation is not possible since the products are highly susceptible to degradation in solvents and on dry flash chromatography columns (little or no separation is achievable by T. L. C. in any case).

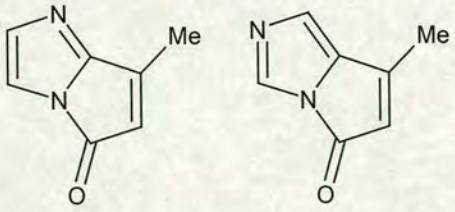
In cases where a single pyrolysis product has been obtained as complete a characterisation as possible has been performed. No element analysis has been performed due to the difficulties incurred when attempting purification by recrystallisation of dry flash chromatography. Accurate mass data is included instead.

FVP of 3-(2*H*-imidazol-1-yl)-acrylic acid methyl ester 254.



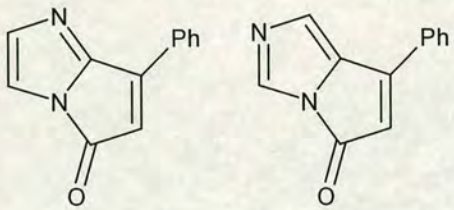
Separate pyrolysis of each isomer under the same conditions (130 mg, T_f 900 °C, T_i 120 °C, P_{range} 0.017-0.065 Torr, *t* 15 min) gave a solid yellow pyrolysate containing pyrrolo[1,2-*a*]imidazol-5-one **233** as the major product and pyrrolo[1,2-*c*]imidazol-5-one **234** as the minor product in an 73 : 27 ratio in each case (80 mg, 78%)[57,56]; *cis*-isomer pyrolysis products δ_{Hmajor} 7.17 (1H, d, ^3J 6.2), 6.95 (1H, s), 6.90 (1H, s) and 5.96 (1H, d, ^3J 6.2); δ_{Hminor} 7.70 (1H, s), 7.26 (1H, d, ^3J 5.9), 6.74 (1H, s) and 5.79 (1H, d, ^3J 5.9); *trans*-isomer pyrolysis products δ_{Hmajor} 7.18 (1H, d, ^3J 6.2), 6.97 (1H, d, *J* 1.8), 6.92 (1H, s) and 5.96 (1H, d, ^3J 6.2); δ_{Hminor} 7.69 (1H, s), 7.25 (1H, d, ^3J 5.9), 6.75 (1H, s) and 5.79 (1H, d, ^3J 5.9).

FVP of 3-(2*H*-imidazol-1-yl)-but-2-enoic acid methyl ester 250.



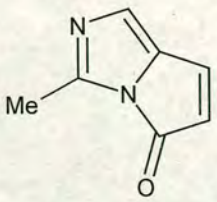
Pyrolysis of the isomer mixture (41 mg, T_f 850 °C, T_i 110 °C, P_{range} 0.020-0.038 Torr, *t* 10 min) gave solid yellow pyrolysate of 7-methylpyrrolo[1,2-*a*]imidazol-5-one **264** as the major product and *7-methylpyrrolo[1,2-c]imidazol-5-one* **265** as the minor product in a 80:20 ratio (with products identified by comparison with the proton NMR spectrum of **264/265**, as described in the discussion section) (25 mg, 76%); δ_{Hmajor} 6.97 (1H, d, ^{n}J 1.5), 6.89 (1H, s), 5.67 (1H, m) and 2.16 (3H, s); δ_{Hminor} 7.67 (1H, s), 6.76 (1H, s), 5.53 (1H, m) and 2.13 (3H, s).

FVP of 3-(2*H*-imidazol-1-yl)-3-phenylacrylic acid methyl ester 246.



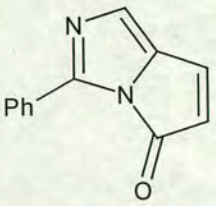
Pyrolysis of the isomer mixture (43 mg, T_f 850 °C, T_i 140 °C, P_{range} 0.012-0.026 Torr, *t* 15 min) gave solid dark yellow pyrolysate of 7-phenylpyrrolo[1,2-*a*]imidazol-5-one **248** and 7-phenylpyrrolo[1,2-*c*]imidazol-5-one **249** in a 80:20 in favour of 7-phenylpyrrolo[1,2-*a*]imidazol-5-one (33mg, 90%)[11,45] δ_{Hmajor} 8.11-8.05 (2H, m), 7.47-7.38 (3H, m), 7.07 (1H, m), 7.02 (1H, m), 6.15 (1H, s); δ_{Hminor} 7.80 (1H, s), 7.65-7.61 (2H, m) and 6.01 (1H, s), other signals overlapping.

3-Methylpyrrolo[1,2-*c*]imidazol-5-one 267.



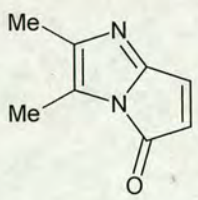
Pyrolysis of 3-(2-methylimidazol-1-yl)-acrylic acid methyl ester (65 mg, T_f 875 °C, T_i 120 °C, P_{range} 0.020-0.065 Torr, *t* 7 min) gave a solid yellow pyrolysate of *3-methylpyrrolo[1,2-c]imidazol-5-one* **267** (47 mg, 88%), decomposes above 195 °C (Found: M^+ 134.0479. $C_7H_6N_2O$ requires *M* 134.0480); δ_H 7.21 (1H, d, ^{3}J 5.7), 6.60 (1H, s), 5.75 (1H, d, ^{3}J 5.7) and 2.44 (3H, s); δ_C 163.54 (quat), 147.96 (quat), 137.11, 134.93 (quat), 126.15, 122.55 and 13.86; *m/z* 134 (M^+, 100%), 105 (19), 79 (38) and 42 (100).

3-Phenylpyrrolo[1,2-*c*]imidazol-5-one 268.



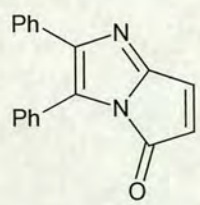
Pyrolysis of 3-(2-phenylimidazol-1-yl)-acrylic acid methyl ester (48 mg, T_f 850 °C, T_i 180 °C, P_{range} 0.019-0.085 Torr, *t* 9 min) gave yellow oil of *3-phenylpyrrolo[1,2-c]imidazol-5-one* **268** (36 mg, 88%), which was not prepared on such a scale as to allow accurate boiling point measurement (Found: M^+ 196.0635. $C_{12}H_8N_2O$ requires *M* 196.0636); δ_H 8.37-8.30 (2H, m), 7.49-7.41 (3H, m), 7.31 (1H, d, ^3J 5.9), 6.88 (1H, s) and 5.87 (1H, d, ^3J 5.9); δ_C 163.26 (quat), 150.27 (quat), 136.84 (CH), 131.17 (CH), 128.33 (2CH), 128.19 (2CH), 127.58 (quat), 127.08 (CH), 122.58 (CH), one quaternary overlapping; *m/z* 196 (M^+, 65%), 168 (100), 141 (35) and 114 (39).

2,3-Dimethylpyrrolo[1,2-*a*]imidazol-5-one 269.



Pyrolysis 3-(4,5-dimethylimidazol-1-yl)-acrylic acid methyl ester (40 mg, T_f 850 °C, T_i 80 °C, P_{range} 0.020-0.075 Torr, *t* 9 min) gave solid red *2,3-dimethylpyrrolo[1,2-a]imidazol-5-one* **269** (38 mg, 95%), decomposes above 205 °C (Found: M^+ 148.0634. $C_8H_8N_2O$ requires *M* 148.0636); δ_H 7.08 (1H, d, ^3J 6.0), 5.88 (1H, d, ^3J 6.0), 2.21 (3H, s) and 2.06 (3H, s); δ_C 164.10 (quat), 153.34 (quat), 139.94 (quat), 136.42 (CH), 126.55 (CH), 11.95 (CH_3) and 8.47 (CH_3); *m/z* 180 (M^+, 78%), 133 (18), 107 (13) and 79 (49).

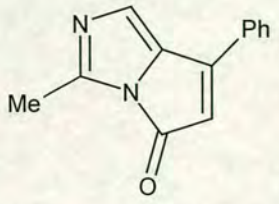
2,3-Diphenylpyrrolo[1,2-*a*]imidazol-5-one 270.



Pyrolysis of 3-(4,5-diphenylimidazol-1-yl)-acrylic acid methyl ester (76 mg, T_f 825 °C, T_i 230 °C, P_{range} 0.010-0.100 Torr, *t* 14 min) gave red oil of *2,3-diphenylpyrrolo[1,2-a]imidazol-5-one* **270** (63 mg, 93%), which was not prepared on such a scale as to allow accurate boiling point measurement (Found: M^+ 272.0944. $C_{18}H_{12}N_2O$ requires *M* 272.0949); δ_H 7.55-7.46 (5H, m), 7.40-7.36 (2H, m), 7.29-7.23 (4H, m) and 6.02 (1H, d, ^3J 6.1); δ_C 163.31 (quat), 154.56 (quat), 143.56 (quat), 132.93 (quat), 129.17 (2CH), 128.55 (quat), 128.40, 128.35 (2CH), 128.22 (2CH),

127.90, 127.74, 127.61, 127.42 (2CH) and 127.18 (quat); *m/z* 272 (M^+, 15%), 244 (15), 165 (6), 121 (10) and 84 (100).

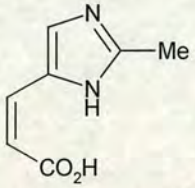
3-Methyl-7-phenylpyrrolo[1,2-*c*]imidazol-5-one 266.



Pyrolysis 3-(2-methylimidazol-1-yl)-3-phenylacrylic acid methyl ester (42 mg, T_f 875 °C, T_i 160 °C, P_{range} 0.010-0.060 Torr, *t* 10 min) gave solid yellow *3-methyl-7-phenylpyrrolo[1,2-c]imidazol-5-one* **266** (33 mg, 91%), decomposes above 200 °C (Found: M^+ 210.0793. $C_{13}H_{10}N_2O$ requires *M* 210.0793); δ_H 7.72-7.67 (2H, m), 7.57-7.48 (3H, m), 7.02 (1H, s), 6.06 (1H, s) and 2.59 (3H, s); δ_C 163.44 (quat), 151.32 (quat), 147.56 (quat), 133.93 (quat), 131.74, 130.02 (quat), 129.12 (2CH), 127.32 (2CH), 126.58, 114.27 and 13.94 (CH_3); *m/z* 210 (M^+, 21%), 182 (14), 169 (29), 154 (10), 140 (49), 128 (28), 114 (62), 102 (78) and 42 (100).

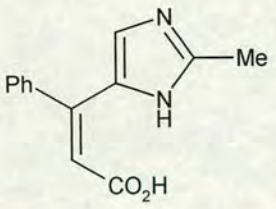
3.3.3 Ring-opening reactions of pyrrolo[1,2-*c*]imidazol-5-ones

***cis*-3-(2-Methyl-3*H*-imidazol-4-yl)-acrylic acid 278.**



FVP of 3-(2-methylimidazol-1-yl)-acrylic acid methyl ester **255** (105 mg, T_f 875 °C, T_i 120 °C, P_{range} 0.020-0.065 Torr, *t* 15 min) gave solid a yellow pyrolysate of 3-methylpyrrolo[1,2-*c*]imidazol-5-one **267** as described above. The entire crude pyrolysate was dissolved in a mixture of tetrahydrofuran (2 cm^3) and water (10 cm^3) then transferred to a round bottomed flask and heated under reflux for 3 h during which time decolourisation occurred. Tetrahydrofuran and water were removed using a rotary evaporator and the product was dried under vacuum (oil pump) for 4 h to afford *cis-3-(2-methyl-3H-imidazol-4-yl)-acrylic acid* **278** (85 mg, 89% for the two steps) decomposes above 190 °C with gas evolution (Found: M^+ 152.0587. $C_7H_8N_2O_2$ requires *M* 152.0586); δ_H ([$^2H_6$]DMSO) 7.52 (1H, s), 6.81 (1H, d, ^3J 12.8), 5.62 (1H, d, ^3J 12.8) and 2.39 (3H, s); δ_C 167.24 (quat), 144.95 (quat), 133.90 (quat), 129.98, 122.21, 118.31 and 13.27 (CH_3); *m/z* 152 (M^+, 90%), 135 (81), 134 (77), 108 (61), 107 (97), 106 (100), 105 (62) and 79 (67).

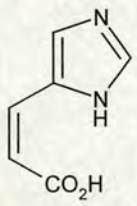
***cis*-3-(2-Methyl-3*H*-imidazol-4-yl)-3-phenylacrylic acid 279.**



FVP of 3-(2-methylimidazol-1-yl)-3-phenyl acrylic acid methyl ester **253** (105 mg, T_f 875 °C, T_i 160 °C, P_{range} 0.010-0.060 Torr, t 15 min) gave solid yellow 3-methyl-7-phenyl-pyrrolo[1,2-*c*]imidazole-5-one **266** as described above. The entire crude pyrolysate was dissolved in a mixture of tetrahydrofuran (2 cm^3) and water (10 cm^3) then transferred to a round bottomed flask and heated under reflux for 6 h during which time decolourisation occurred. Tetrahydrofuran and water were removed using a rotary evaporator and the product was dried under vacuum (oil pump) for 4 h to afford *cis-3-(2-methyl-3H-imidazol-4-yl)-3-phenylacrylic acid* **279** (71 mg, 72% for the two steps) decomposes above 170 °C with gas evolution (Found: M^+ 228.0895. $C_{13}H_{12}N_2O_2$ requires M 228.0898); δ_H ([$^2H_6$]DMSO) 7.70-7.62 (5H, m, br), 7.14 (1H, s), 5.85 (1H, s) and 2.68 (3H, s); δ_C 167.48 (quat), 145.66 (quat), 143.51 (quat), 141.34 (quat), 136.05 (quat), 129.57, 129.33 (2CH), 129.15 (2CH), 122.57, 121.26 and 13.88 (CH_3); *m/z* 228 (M^+, 42%), 210 (27), 183 (70), 182 (100), 181 (72), 169 (57), 168 (60), 128 (63), 115 (63) and 114 (61).

Synthesis of *cis*-3-(3*H*-imidazol-4-yl)-acrylic acid (*cis*-urocanic acid) 276.

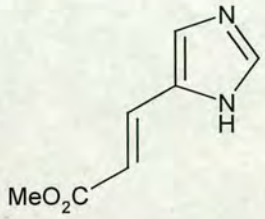
Attempted synthesis of *cis*-urocanic acid 276 from *trans*-urocanic acid 275.



FVP of *trans*-urocanic acid (100 mg, 7.2 mmol, T_f 850 °C, T_i 220 °C, P_{range} 0.010-0.040 Torr, t 15 min) gave a solid yellow pyrolysate that was partially dissolved into a solution of tetrahydrofuran (2 cm^3) and water (10 cm^3) then transferred to a round bottomed flask and heated under reflux for 4 h during which time no decolourisation occurred. Tetrahydrofuran and water were removed using a rotary evaporator and the product dried under vacuum (oil pump) for 4 h to afford the crude reaction mixture. A large proportion of the crude product was insoluble in [$^2H_6$]DMSO but a proton NMR of the soluble crude showed only small quantities of *cis*-urocanic acid **276** to be present. A second pyrolysis was performed under the same conditions and the products collected on a cold-finger trap. The connection between the furnace tube and

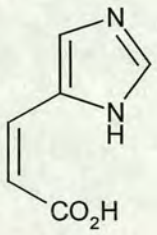
cold finger was wrapped in tin foil to maximise product condensation on the cold surface of the trap. The products were rinsed from the cold finger, under nitrogen, into a minimum volume of acetone (20 cm^3) and were transferred to a round bottom flask. The acetone was removed at the oil pump whilst maintaining the solution temperature below 0 °C. A yellow solid was obtained and immediately treated with THF/water solution as before. Again insoluble products were present. Subsequent heating and concentration gave very little *cis*-urocanic acid product.

trans-3-(3_H_-Imidazol-4-yl)-acrylic acid methyl ester 240.



trans-Urocanic acid (2.00 g, 14.5 mmol) was dissolved in warm methanolic hydrogen chloride solution (23%w/v, 25 cm^3) and the solution heated under reflux for 3 h. The solution was left to stand for 48 h during which time white crystalline product precipitated. The product was collected by filtration. The filtrate was concentrated and dissolved in water (100 cm^3) and treated with potassium hydroxide (1 M, 15 cm^3) then continuously extracted with dichloromethane over 24 h. The extract was dried ($MgSO_4$) and the solvent removed under reduced pressure to give a second crop of *trans*-3-(3*H*-imidazol-4-yl)-acrylic acid methyl ester **240** (1.76 g, 80%)[48] mp 93-95 °C [lit.,1[09] 94-96 °C] δ_H 7.65 (1H, s), 7.55 (1H, d, ^3J 15.6), 7.23 (1H, s), 6.42 (1H, d, ^3J 15.6) and 3.72 (3H, s).

cis-3-(3_H_-imidazol-4-yl)-acrylic acid (_cis_-urocanic acid) 276.



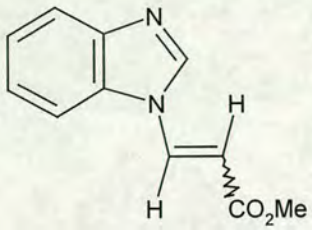
A small scale pyrolysis of *trans*-methyl urocanate **240** (30 mg, 0.2 mmol, T_f 850 °C, T_i 220 °C, P_{range} 0.010-0.040 Torr, t 7 min) was performed using a cold-finger trap to collect the product. Due to the instability of pyrrolo[1,2-*c*]imidazol-5-one **234** in air, which led to the formation of insoluble material, the pyrolysate was frozen into deuteriated chloroform and the trap allowed to warm to room temperature under nitrogen. A proton NMR spectrum showed the pyrolysate to be pyrrolo[1,2-*c*]imidazol-5-one[57] **234**; δ_H 7. 73 (1H, s), 7.30 (1H, dd, ^3J 5.9 and ^4J 0.8), 6.79 (1H, s) and 5.83 (1H, d, ^3J 5.9). A preparative pyrolysis of *trans*-3-(3*H*-imidazol-4-yl)-acrylic acid methyl ester **240** (312 mg, 20 mmol, T_f 850 °C, T_i 220 °C, P_{range} 0.010-

0.060 Torr, *t* 20 min) under the same conditions gave solid yellow pyrrolo[1,2-*c*]imidazol-5-one **234** that was frozen into a mixture of tetrahydrofuran (2 cm^3) and water (10 cm^3) to prevent any degradation of the pyrrolo[1,2-*c*]imidazol-5-one **234** and control the ring-opening reaction. The cold-finger was allowed to warm to room temperature under nitrogen then the pyrrolo[1,2-*a*]imidazol-5-one in THF/water solution transferred to a round bottomed flask and heated under reflux for 45 min during which time the colour faded. The solvent was removed using a rotary evaporator then dried at the oil pump for 3 h to afford *cis*-urocanic acid **276** as off-white solid (220 mg, 78%)[110] mp 169-171 °C [lit.,[110] 171-173 °C] δ_H ([$^2H_6$]DMSO) 8.16 (1H, s), 7.67 (1H, d, ^nJ 0.9), 6.88 (1H, d, ^3J 12.9) and 5.68 (1H, d, ^3J 12.9).

3.4 Synthesis of azabenzopyrrolizin-3-ones

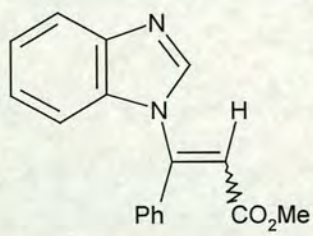
3.4.1 Synthesis of azabenzopyrrolizin-3-one precursors

3-(Benzimidazol-1-yl)-acrylic acid methyl ester 291.



Propynoic acid methyl ester (4.20 g, 50 mmol) was added dropwise to a stirred solution of benzimidazole (5.90 g, 50 mmol) in tetrahydrofuran (40 cm^3) and heated under reflux for 4 h. The solution was allowed to stir overnight. The solvent was removed under reduced pressure and the crude product recrystallised from toluene (15 cm^3) to afford 3-(benzimidazol-1-yl)-acrylic acid methyl ester **291** as a 44 : 56 *E/Z* isomer mixture (9.58 g, 95%)[111] mp 102-104 °C [lit,[111] *cis* 95.5-96.5 °C, *trans* 111.0-112.0 °C]; δ_H 9.09 ($1H_{cis}$, s), 8.06 ($1H_{trans}$, s), 7.96 ($1H_{trans}$, d, ^3J 14.5), 7.74-7.69 (2H, m), 7.53-7.49 ($1H_{trans}$, m), 7.31-7.21 (5H, m), 6.94 ($1H_{cis}$, d, ^3J 10.4), 6.14 ($1H_{trans}$, d, ^3J 14.5), 5.52 ($1H_{cis}$, d, ^3J 10.4), 3.70 ($3H_{trans}$, s) and 3.67 ($3H_{cis}$, s); $\delta_{C(cis \text{ and } trans)}$ 166.47 (quat), 164.89 (quat), 144.16 (quat), 143.93, 142.61 (quat), 141.30, 135.30, 133.11 (quat), 131.77 (quat), 130.26, 124.65, 124.02, 123.97, 123.62, 120.79, 120.41, 110.81, 109.16, 105.76, 105.02, 51.69 (CH_3) and 51.58 (CH_3); *m/z* 202 (M^+, 82%), 187 (35), 172 (43), 171 (100), 170 (40), 159 (37), 145 (73), 144 (57), 143 (60), 142 (67), 129 (48) and 118 (51).

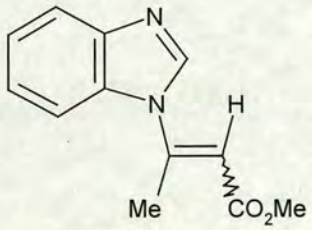
3-(Benzimidazol-1-yl)-3-phenylacrylic acid methyl ester 293.



2,3-Dibromo-3-phenylpropionic acid methyl ester **252** (~3.4 g, 10 mmol) was prepared (see section **3.3.1**) and added to a solution of benzimidazole (1.24 g 10 mmol) and triethylamine (5.0 g) in toluene (100 cm^3) and heated under reflux for 1.5 h. The solution was concentrated to afford a crude reaction mixture that was dissolved into ether to precipitate unreacted benzimidazole. After filtration the organic phase was washed with water (2 × 40 cm^3), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the product (2.13 g, 101%). The product was identified as α-bromo-

cinnamic acid methyl ester **292** by ^{1}H NMR and mass spectroscopy δ_H 8.22 (1H, s), 7.87-7.83 (2H, m), 7.44-7.40 (3H, m) and 3.90 (3H, s); *m/z* 242 and 240 (M^+, 36 and 38%), 211 (22), 209 (22), 183 (20), 181 (21), 162 (40), 161 (100) 129 (71) and 102 (98).[78] This product was dissolved in toluene (100 cm^3) and benzimidazole (1.24 g, 10 mmol) was added and the solution was then heated under reflux for 24 h. The crude reaction was extracted with dichloromethane (3 × 30 cm^3) and the organic extracts were washed with water (50 cm^3) and dried over magnesium sulfate. Removal of the magnesium sulfate by filtration and concentration of the filtrate under reduced pressure afforded crystallisation of the crude product which recrystallised from a minimum volume of toluene (20 cm^3) to give *3-(benzimidazol-1-yl)-3-phenylacrylic acid methyl ester*, **293** (0.49 g, 21%) mp 127-129 °C; (Found: M^+ 278.1051 $C_{17}H_{14}N_2O_2$ requires *M* 278.1055); δ_H 8.00 (1H, s), 7.83 (1H, dt, ^3J 8.0, ^4J 0.9), 7.51-7.41 (2H, m), 7.40-7.34 (2H, m), 7.31-7.22 (2H, m), 7.13 (1H, td, ^3J 7.7, ^4J 1.2), 6.80 (1H, dt, ^3J 8.0, ^4J 0.9), 6.43 (1H, s) and 3.59 (3H, s); δ_C 164.09 (quat), 146.04 (quat), 143.90, 143.51(quat), 134.58 (quat), 133.49 (quat), 131.42, 129.02 (2C), 127.48 (2C), 123.46, 122.65, 120.38, 113.09, 111.30 and 51.71 (CH_3); *m/z* 278 (M^+, 51%), 263 (24), 247 (23), 219 (31), 161 (21), 118 (27) and 91 (100).

Attempted synthesis of 3-(benzimidazol-1-yl)-but-2-enoic acid methyl ester 294.

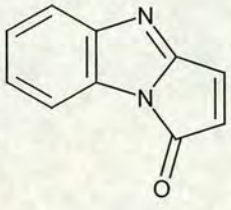


2,3-Dibromobutyric acid methyl ester (2.00 g, 77.5 mmol) (see section **3.3.1**) and benzimidazole (0.92 g, 77.5 mmol) were added together with triethylamine (4.0 g, 0.04 mol) to toluene (40 cm^3) and heated under reflux for ~30 h. The solution was concentrated to afford a crude reaction mixture that was dissolved into ether to precipitate unreacted benzimidazole. After filtration the organic phase washed with water (100 cm^3) and dried over magnesium sulfate. This product was distilled using a Kugelrohr oven to give impure *3-(benzimidazol-1-yl)-but-2-enoic acid methyl ester* **294** (20 mg, 1%). δ_H 8.11 (1H, s), 6.20 (1H, s), 3.79 (3H, s) and 2.80 (3H, s) (other signals indistinguishable).

Alternative route to 3-(benzimidazol-1-yl)-but-2-enoic acid methyl ester 294. Benzimidazole (0.12 g, 1 mmol) and but-2-ynoic acid methyl ester (0.098 g, 1 mmol) were added together in toluene and heated under reflux for 18 h. A small sample was removed from the solution and the solvent removed under reduced pressure then the residue was analysed by proton NMR spectroscopy. Both starting material and products were present. A second equivalent of methyl 2-butynoate was added and the reaction heated under reflux for a further 12 h after which a second proton NMR spectrum showed no further reaction had occurred. The excess methyl 2-butynoate and solvent was removed using a rotary evaporator to afford largely starting materials and a small amount of product. The crude reaction mixture was extracted into DCM (3×80 cm^3), dried over $MgSO_4$ and concentrated to give an impure (containing benzimidazole) 50:50 *E/Z* isomer mixture of *3-(benzimidazol-1-yl)-but-2-enoic acid methyl ester* **294** (~5 mg, 1-2%). Assignment of geometry to either of the isomers was not possible. Identifiable signals for each isomer; δ_H 8.12 (1H, s), 6.21 (1H, s), 3.80 (3H, s) and 2.82 (3H, s); δ_H 7.95 (1H, s), 6.07 (1H, s), 3.53 (1H, s) and 2.39 (1H, s) (other signals indistinguishable for both isomers).

3.4.2 Synthesis of azabenzopyrrolizin-3-ones by flash vacuum pyrolysis

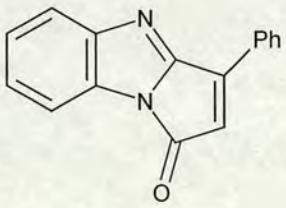
Pyrrolo[1,2-*a*]benzimidazol-1-one 280.



Small scale pyrolyses (50 mg, 0.25 mmol, T_i 50-200 °C, P_{range} 0.01-0.05 Torr, t 12 min) of 3-(benzimidazol-1-yl)-acrylic acid methyl ester **291** were performed at furnace temperatures of 850, 900 and 950 °C. The optimum temperature for complete conversion of start material was 950 °C and resulted in a solid yellow pyrolysate. A proton NMR spectrum allowed identification of the pyrolysate as pyrrolo[1,2-*a*]benzimidazol-1-one **280**. Large scale pyrolysis involved several complications: poor volatility of the substrate resulted in some degradation due to the elevated temperatures required for sublimation, thermal degradation of products at furnace exit/trap was apparent and an insoluble white side-product was found to be present in the pyrolysate. A series of pyrolyses on a 100 mg scale showed that an increase of inlet temperature lead to an increased pyrolysis rate

(and notable increase in pressure) but more degradation of the substrate and larger amounts of insoluble side-product. Ideal system conditions were found to be a dry ice/acetone cold-finger trap that stopped thermal degradation of the pyrolysate and slow sublimation of the substrate at inlet at temperature of 115 °C (to minimise precursor degradation and side-product formation). A large scale pyrolysis was performed under optimised conditions (0.50 g, 2.5 mmol, T_i 115 °C, P_{range} 0.01-0.10 Torr, t 105 min) after which the pyrolysate was rinsed from the cold trap surface under a dry nitrogen atmosphere into dry ether. The crude product was absorbed onto silica and purified by dry flash chromatography (70% ethyl acetate in hexane) to give *pyrrolo[1,2-a]benzimidazol-1-one* **280** (0.30 g, 71%) mp 106-108 °C; (Found: M^+ 170.0481 $C_{10}H_6N_2O$ requires M 170.0480); δ_H 7.62 (2H, dd, ^3J 7.8 and 4.2), 7.35-7.12 (2H, m), 7.24 (1H, d, ^3J 6.1) and 6.27 (1H, d, ^3J 6.1); δ_C 162.36 (quat), 159.24 (quat), 148.90 (quat), 135.04, 132.64, 129.93 (quat), 127.18, 124.39, 121.78 and 111.74; *m/z* 170 (M^+, 31%), 143 (15), 142 (100), 118 (25), 115 (32), 114 (13), 102 (15), 91 (11) and 88 (11).

3-Phenylpyrrolo[1,2-*a*]benzimidazol-1-one 295.



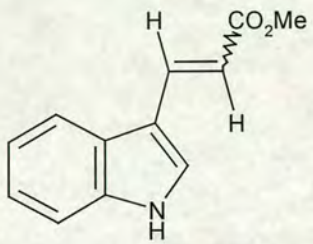
Small scale pyrolyses (25 mg, 0.09 mmol, T_i 50-180 °C, P_{range} 0.01-0.04 Torr, t 12 min) of 3-(benzimidazol-1-yl)-3-phenylacrylic acid methyl ester **293** were performed at furnace temperatures of 925 and 950 °C. The optimum temperature for complete conversion of starting material was 950 °C. A dry ice/acetone cold-finger trap was used for a large scale pyrolysis (92 mg, 0.33 mmol, T_f 950 °C, T_i 50-180 °C, P_{range} 0.03-0.12 Torr, t 23 min) to keep the pyrolysate cold. The furnace exit/trap inlet was wrapped in foil in an attempt to maximise condensation of the product on the cold-finger surface. This was ineffective and most product condensed on the body of the trap at the furnace exit where upon thermal degradation occurred. On completion of the pyrolysis the pyrolysate was rinsed from the trap in dry ether, absorbed onto silica and purified by dry flash chromatography (50% ethyl acetate in hexane) to give *3-phenylpyrrolo[1,2-a]benzimidazol-1-one* **295** (29 mg, 36%) mp 120-122 °C; (Found: M^+ 246.0790 $C_{16}H_{10}N_2O$ requires M 246.0793); δ_H 8.20-8.15 (2H, m), 7.73 (1H, ddd, ^3J 7.9, ^4J 1.1

and ^{n}J 0.7), 7.66 (1H, ddd, ^{3}J 7.9, ^{4}J 1.1 and ^{n}J 0.7), 7.55-7.46 (3H, m), 7.34 (1H, td, ^{3}J 7.6 and ^{4}J 1.2), 7.24 (1H, td, ^{3}J 7.6 and ^{4}J 1.2) and 6.44 (1H, s); δ_C 162.57 (quat), 148.66 (quat), 147.19 (quat), 131.83, 129.77 (quat), 129.04 (2C), 128.56 (quat), 128.24 (2C), 127.05, 125.38 (quat), 124.21, 121.76, 121.70 and 111.83; *m/z* 246 (M^+, 34%), 219 (23), 218 (62), 194 (9), 147 (10), 109 (23) and 86 (100).

3.5. Synthesis of benzopyrrolizin-3-ones

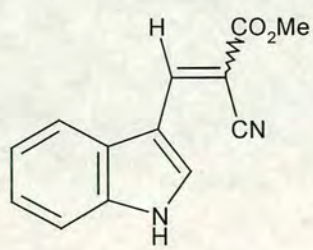
3.5.1 Synthesis of benzopyrrolizin-3-one precursors

3-(1*H*-Indol-3-yl)-acrylic acid methyl ester 298.



Methyl (triphenylphosphoranylidene) acetate (0.67 g, 2 mmol) was added to a solution of indole 3-carboxaldehyde (0.29 g, 2 mmol) in toluene (25 cm^3) and stirred overnight. The crude product was purified by dry flash chromatography on silica using a 15-50% ethyl acetate in hexane eluent gradient to remove triphenylphosphine oxide side-product and afford isolated *E* and *Z* isomers of 3-(1*H*-indol-3-yl)-acrylic acid methyl ester **298** (0.35 g, 88%, 0.31 g *trans*, 0.04 g *cis*)[112] mp_{trans} 152-153 °C [lit.,[113] 153-154 °C] and mp_{cis} 162-164 °C (lit.,[113] 163-164 °C); δ_{Htrans} 8.46 (1H broad, NH), 7.89-7.79 (2H, m), 7.39 (1H, m), 7.32 (1H, d, ^3J 15.7), 7.17-7.10 (2H, m), 6.34 (1H, d, ^3J 15.7) and 3.81 (3H, s); δ_{Hcis} 8.82 (1H, d, ^3J 2.9), 8.57 (1H broad, NH), 7.67 (1H, m), 7.37-7.12 (3H, m), 7.23 (1H, d, ^3J 12.4), 5.77 (1H, d, ^3J 12.4) and 3.71 (3H, s); δ_{Ctrans} 168.41 (quat), 138.60, 137.18 (quat), 129.56, 124.92 (quat), 122.43, 120.70, 119.77, 112.33 (quat), 111.84, 111.41 and 50.91 (CH_3); δ_{Ccis} 168.79 (quat), 138.55, 136.98 (quat), 128.97, 125.14 (quat), 123.18, 121.38, 120.28, 113.31 (quat), 112.62, 111.73 and 51.35 (CH_3); m/z_{trans} 201 (M^+, 97%), 171 (32), 170 (100), 143 (40), 142 (24), 141 (39), 115 (71) and 114 (30); m/z_{cis} 201 (M^+, 96%), 171 (34), 170 (100), 143 (37), 142 (28), 141 (43), 115 (66) and 114 (32).

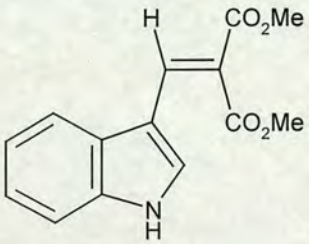
2-Cyano-3-(1*H*-indol-3-yl)-acrylic acid methyl ester 299.



Indole 3-carboxaldehyde (0.72 g, 5 mmol) and methyl cyanoacetate (0.495 g, 5 mmol) were added together in toluene (15 cm^3) with 15 drops of glacial acetic acid and 15 drops of piperidine. The reaction was stirred for 2 h after which à yellow precipitate formed. Toluene was removed using a rotary evaporator and the crude solid dissolved in DCM. Water (75 cm^3) was added and the organic layer separated.

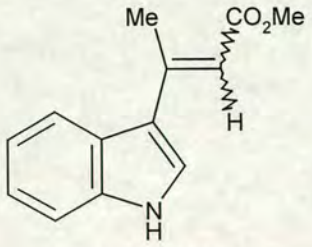
The aqueous layer was then extracted with DCM (3 × 25 cm^3) and the combined organic extracts washed with water (50 cm^3) then dried over $MgSO_4$. The solvent was removed to give 2-cyano-3-(1*H*-indol-3-yl)-acrylic acid methyl ester, **299** (1.10 g, 97%) mp 183-185 °C [lit.,[114] 187-188 °C]; δ_H 9.34 (1H, broad, NH), 8.57 (1H, m) 8.55 (1H, s), 7.77 (1H, m), 7.42 (1H, m), 7.31-7.12 (2H, m) and 3.86 (3H, s); δ_C 164.92 (quat), 147.22, 136.66 (quat), 132.38, 127.89 (quat), 123.99, 122.61, 118.69 (quat), 118.33, 113.13, 110.91 (quat), 92.90 (quat) and 53.00 (CH_3); *m/z* 226 (M^+, 38%), 195 (25), 145 (90), 144 (100), 116 (40) and 89 (45).

2-(1*H*-Indol-3-yl methylene)-malonic acid dimethyl ester 300.



Indole 3-carboxaldehyde (0.72 g, 5 mmol) and dimethyl malonate (0.66 g, 5 mmol) were added together in toluene (15 cm^3) with 15 drops of glacial acetic acid and 15 drops of piperidine. The reaction was stirred for $^3/_4$ h after which the reaction was fitted with a Dean/Stark trap and heated under reflux until red in colour. Upon cooling, water (50 cm^3) was added to the reaction and the organic layer separated. The aqueous phase was then extracted with ether (3 × 25 cm^3), the combined extracts washed with water (50 cm^3) and dried over $MgSO_4$ after which the solvents were removed to give *2-(1H-indol-3-yl methylene)-malonic acid dimethyl ester*, **300** (0.62 g, 48%) mp decomposes >300 °C; (Found: C, 64.8; H, 5.0; N, 4.9. $C_{14}H_{13}NO_4$ requires C, 64.85; H, 5.0; N, 5.0); (Found: M^+ 259.0841. $C_{14}H_{13}NO_4$ requires *M* 259.0845); δ_H 8.85 (1H, broad, NH), 8.16 (1H, s), 7.79-7.76 (2H, m), 7.35 (1H, m), 7.29-7.21 (2H, m) and 3.86 (6H, s); δ_C 168.83 (quat), 166.16 (quat), 136.30, 136.13 (quat), 128.32, 127.87 (quat), 123.84, 122.02, 119.19 (quat), 118.91, 112.14, 110.88 (quat), 53.04 and 52.81; *m/z* 259 (M^+, 100%), 228 (38), 199 (38), 196 (29), 170 (26), 145 (30), 144 (40), 141 (50) and 114 (27).

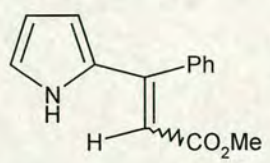
Attempted synthesis of 3-(1*H*-indol-3-yl)-but-2-enoic acid methyl ester 301.



Methyl diethylphosphonoacetate (4.41 g, 21 mmol) was added to a solution of sodium methoxide (0.48 g, 21 mmol in 100 cm^3 methanol) and stirred for 30 min. The mixture was cooled in an ice bath and a solution of 3-acetylindole (1.0 g, 6.3 mmol) in methanol (25 cm^3) added dropwise. The reaction was then heated under reflux for 48 h. Water (100 cm^3) was added to the cooled reaction and the organic components extracted with ether (3 × 50 cm^3), washed with water (50 cm^3) and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a solid 'product' but mass spectrum and proton NMR analysis showed no reaction had occurred and that the only component was recovered 3-acetylindole.

An alternative route was attempted[79] in which indole (2.0 g, 17 mmol) and acetoacetic acid methyl ester (4.64 g, 40 mmol) were added with conc. hydrochloric acid to ethanol (12 cm^3) and the reaction allowed to stand overnight. The reaction became deep red in colour and was extracted with ether (3 × 50 cm^3), washed with water (100 cm^3) and dried over $MgSO_4$. A viscous yellow liquid product was obtained (3.76 g), which was shown by its mass spectrum and proton NMR spectrum to be undesired products which were not identified.

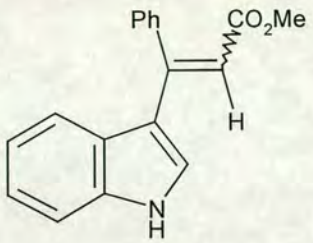
3-(Pyrrol-2-yl)-3-phenylacrylic acid methyl ester.



Pyrrole (67 mg, 1 mmol) and methyl phenylpropiolate (160 mg, 1 mmol) were added together in glacial acetic acid (15 cm^3) with palladium (II) acetate (5 mg, 2% cat) and the reaction allowed to stir at room temperature whereupon an immediate colour change to dark yellow occurred. The reaction was followed by proton NMR spectroscopy and went to completion in 10 h. Glacial acetic acid was removed using a rotary evaporator and the product purified by dry flash chromatography (5% DCM in hexane) to give *3-(pyrrol-2-yl)-3-phenylacrylic acid methyl ester* as a pale yellow solid (158 mg, 69%) mp 57-59 °C; (Found: M^+ 227.0945. $C_{14}H_{13}NO_2$ requires *M* 227.0946); δ_H 7.32-7.26 (5H, m), 6.99 (1H, m),

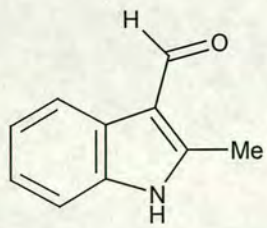
6.13 (1H, m), 6.01 (1H, m), 5.50 (1H, s) and 3.70 (3H, s); δ_C 169.44 (quat), 149.54 (quat), 142.57 (quat), 130.40 (quat), 129.00 (2CH), 128.36, 127.95 (2CH), 123.08, 119.30, 109.92, 109.26 and 51.92 (CH_3); *m/z* 227 (M^+, 100%), 196 (43), 195 (31), 169 (18), 168 (30), 167 (87), 166 (15), 154 (11), 139 (15) and 84 (30).

3-(1*H*-Indol-3-yl)-3-phenylacrylic acid methyl ester 302.



Indole (0.234 g, 2 mmol) and phenylpropynoic acid methyl ester (0.320 g, 2 mmol) were added together in glacial acetic acid (25 cm^3) with palladium (II) acetate (9 mg, 2% cat) and the reaction allowed to stir at room temperature for 30 h. The crude product was absorbed onto silica and purified by dry flash chromatography (10-40% ethyl acetate in hexane eluent gradient) then crystallised by evaporation of DCM at atmospheric pressure to give 15:85 isomer mixture of *3-(1H-indol-3-yl)-3-phenylacrylic acid methyl ester* **302** (0.477 g, 89%). The isomers were not separated and neither isomer could be assigned specific geometry; mp 159-161 °C; (Found: M^+ 277.1099. $C_{18}H_{15}NO_2$ requires *M* 277.1103); δ_{Hmajor} 8.58 (1H, broad, NH), 7.73 (1H, m), 7.31-7.24 (6H, m), 7.19-7.14 (2H, m), 6.70 (1H, d, ^3J 2.9), 6.52 (1H, s) and 3.57 (3H, s); δ_{Hminor} 8.52 (1H, broad, NH), 7.07 (1H, m), 6.92-6.89 (2H, m), 6.19 (1H, s) and 3.65 (3H, s) (other signals indistinguishable); δ_{Cmajor} 167.60 (quat), 153.32 (quat), 140.16 (quat), 137.25 (quat), 129.77, 128.88 (2CH), 127.96, 127.84 (2CH), 125.08 (quat), 123.07, 121.41, 120.83, 118.55 (quat), 112.03, 111.39 and 51.14 (CH_3); *m/z* 277 (M^+, 100%), 246 (80), 219 (25), 218 (27), 217 (42), 216 (23), 204 (13), 191 (18), 189 (21), 165 (5), 144 (18) and 109 (20).

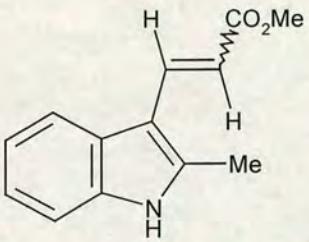
2-Methyl-1*H*-indole-3-carboxaldehyde 313.



Phosphorus oxychloride (1.44 g, 0.88 cm^3, 9.4 mmol) was added to ice cooled *N,N*-dimethylformamide (2.74 g, 2.88 cm^3, 37.4 mmol) at 0-5 °C and stirred for 2.5 h to give the formylation complex. A solution of 2-methylindole (1.12 g, 8.5 mmol) in *N,N*-dimethylformamide (5 cm^3) was added dropwise, keeping the reaction temperature below 5 °C. Upon completion of the

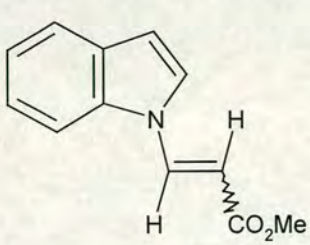
addition, ice (7 g) was added followed by sodium hydroxide (3.75 g in 10 cm^3 water), dropwise, to give a dull yellow precipitate. The reaction was then heated under reflux for 1 h and refrigerated overnight, during which time precipitation of crude product occurred. The product was filtered, washed with water (450 cm^3) and re-filtered to give 2-methyl-1*H*-indole-3-carboxaldehyde, **313** (1.10 g, 81%)[115] mp 199-200 °C [lit.,[115] 199-200 °C]; δ_H 12.01 (1H, broad, NH), 10.06 (1H, s), 8.07 (1H, m), 7.40 (1H, m), 7.21-7.13 (2H, m) and 2.69 (3H, s); δ_C 184.43, 148.77 (quat), 135.52 (quat), 125.75 (quat), 122.82, 122.07, 120.16, 113.82 (quat), 111.56 and 11.63 (CH_3); *m/z* 159 (M^+, 96%), 158 (100), 157 (17), 130 (32), 103 (16) and 77 (16).

3-(2-Methyl-1*H*-indol-3-yl)-acrylic acid methyl ester 312.



2-Methyl-1*H*-indole-3-carboxaldehyde **313** (0.5 g, 3 mmol) and methyl (triphenylphosphoranylidene)acetate (1.05 g, 3 mmol) were added together in toluene (15 cm^3) and heated under reflux for 24 h. Toluene was removed using a rotary evaporator and the product purified by dry flash chromatography on silica (20% ethyl acetate in hexane) to give *trans*-3-(2-methyl-1*H*-indol-3-yl)-acrylic acid methyl ester **312** (0.62 g, 93%) identified by propenoate carbon-carbon double bond coupling constants; mp 153-154 °C [lit.,[115] 154-155 °C]; δ_H 8.64 (1H, broad, NH), 8.05 (1H, d, ^3J 15.8), 7.93 (1H, m), 7.42-7.26 (3H, m), 6.52 (1H, d, ^3J 15.8), 3.92 (3H, s) and 2.60 (3H, s); δ_C 169.14 (quat), 140.21 (quat), 137.78, 135.63 (quat), 126.19 (quat), 122.34, 121.30, 119.80, 111.31, 110.82, 109.40 (quat), 51.30 (CH_3) and 12.16 (CH_3); *m/z* 215 (M^+, 100%), 184 (80), 183 (22), 156 (44), 155 (33), 154 (37), 128 (18), 129 (18), 78 (30) and 77 (41).

3-(Indol-1-yl)-acrylic acid methyl ester 314.

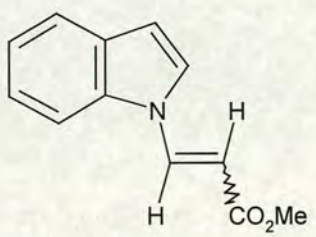


Indole (2.93 g, 25 mmol) and *trans*-dichlorobis(triphenylphosphine)palladium (II) (350 mg) were added together in triethylamine (125 cm^3) in a three-neck round bottomed flask with light protection, and the system placed under a nitrogen atmosphere.

Propynoic acid methyl ester (4.20 g, 50 mmol) was added dropwise, with stirring, from a pressure-equalised dropping-funnel and the mixture then heated under reflux overnight.[116] Triethylamine was removed using a rotary evaporator and the crude product purified by dry flash chromatography on silica (15% ethyl acetate in hexane) to give a 76:24 *E*/*Z* isomer mixture of *3-(indol-1-yl)-acrylic acid methyl ester* **314** as a white solid (1.23 g, 25%) mp 81-83 °C; (Found: M^+ 201.0787. $C_{12}H_{11}NO_2$ requires *M* 201.0790); δ_{Htrans} 8.24 (1H, d, ^3J 14.1), 7.59-7.49 (2H, m), 7.30 (1H, d, ^3J 3.4), 7.32-7.16 (2H, m), 6.67 (1H, d, ^3J 3.4), 5.90 (1H, d, ^3J 14.1) and 3.79 (3H, s); δ_{Hcis} 8.47 (1H, d, ^3J 3.7), 6.59 (1H, d, ^3J 3.7), 5.32 (1H, d, ^3J 11.0) and 3.69 (3H, s) (other signals indistinguishable); δ_{Ctrans} 167.71 (quat), 137.16, 135.94 (quat), 129.65 (quat), 123.80, 123.35, 122.34, 121.36, 109.88, 108.70, 99.97 and 51.45 (δ_{Ccis} signals too weak for identification); *m/z* 201 (M^+, 100%), 171 (14), 170 (87), 143 (11), 142 (11), 117 (12), 115 (15) and 85 (10).

In a similar reaction two equivalents of propynoic acid methyl ester (0.84 g, 10 mmol) were added to a solution of indole (0.58 g, 5mmol) and *trans*-dichlorobis(triphenylphosphine)palladium (II) (30 mg) in triethylamine (30 cm^3) and the mixture treated under the previous conditions. Triethylamine was removed using a rotary evaporator and the crude product partitioned between DCM and water (100 cm^3) added. The organic layer was separated and the aqueous extracted with ether (3 × 50 cm^3), washed with water (50 cm^3) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the mixture distilled to give *3-(indol-1-yl)-acrylic acid methyl ester* **314** (0.31 g, 31%) bp 72-74 °C (0.9 Torr) spectrum as above.

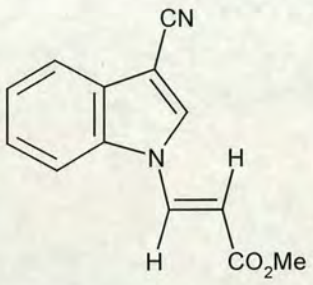
3-(Indol-1-yl)-acrylic acid methyl ester 314.



To a solution of indole (58.5 mg, 0.5 mmol) and propynoic acid methyl ester (42 mg, 0.5 mmol) in tetrahydrofuran (3 cm^3) was added, dropwise, tetrabutylammonium fluoride (0.5 cm^3 of 1 M solution in tetrahydrofuran, 0.5 mmol). The reaction was allowed to stir at room temperature for 30 min. Water (10 cm^3) was added and the organic components extracted into ethyl acetate (3 × 20

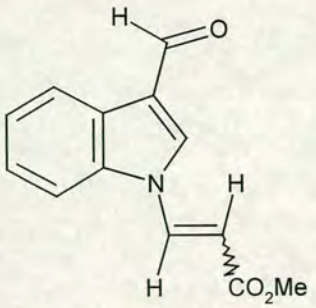
cm^3), washed with water (5 cm^3) and dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded a 67:33 *E/Z* isomer mixture of 3-(indol-1-yl)-acrylic acid methyl ester **314** that was purified by distillation (96 mg, 96%); mp 81-83 °C, bp 170 °C (0.9 Torr); δ_{Htrans} 8.21 (1H, d, ^3J 14.1), 7.59-7.47 (2H, m), 7.30 (1H, d, ^3J 3.4), 7.29-7.11 (2H, m), 6.64 (1H, d, ^3J 3.4), 5.88 (1H, d, ^3J 14.1) and 3.74 (3H, s); δ_{Hcis} 8.46 (1H, d, ^3J 3.7), 6.58 (1H, d, ^3J 3.7), 5.31 (1H, d, ^3J 11.0) and 3.69 (3H, s) (other signals indistinguishable) (data compatible with authentic sample).[116]

3-(3-Cyanoindol-1-yl)-acrylic acid methyl ester 318.



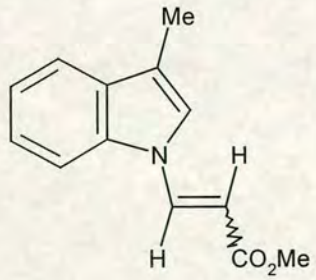
3-Cyanoindole (142 mg, 1.0 mmol) and propynoic acid methyl ester (84 mg, 1.0 mmol) were dissolved in tetrahydrofuran (3 cm^3) and tetrabutylammonium fluoride (1 cm^3 of 1 M solution in tetrahydrofuran, 1.0 mmol) was added dropwise with stirring. The reaction was allowed to stir at room temperature for 30 min after which water (20 cm^3) was added and the organic components extracted into ethyl acetate (3 × 40 cm^3), washed with water (10 cm^3) and dried over $MgSO_4$. The solution was concentrated by rotary evaporation and the crude solid recrystallised from the minimum volume of ethyl acetate (3 cm^3) to give *trans-3-(3-cyanoindol-1-yl)-acrylic acid methyl ester* **318** as pale yellow needles (214 mg, 95%) mp 141-143 °C; (Found: C, 69.25; H, 4.6; N, 12.2. $C_{13}H_{10}N_2O_2$ requires C, 69.0; H, 4.45; N, 12.4); (Found: M^+ 226.0741. $C_{13}H_{10}N_2O_2$ requires *M* 226.0742); δ_H 8.15 (1H, d, ^3J 14.2), 7.85 (1H, s), 7.71 (1H, d, ^3J 7.7), 7.59 (1H, d, ^3J 7.7), 7.40 (1H, td, ^3J 7.6 and ^4J 1.3), 7.34 (1H, td, ^3J 7.6 and ^4J 1.3), 6.09 (1H, d, ^3J 14.2) and 3.78 (3H, s); δ_C 166.35 (quat), 135.66, 134.94 (quat) 130.22, 127.64 (quat), 125.77, 124.11, 120.21, 113.89 (quat), 110.68, 105.10, 92.78 (quat) and 51.88 (CH_3); *m/z* 226 (M^+, 100%), 197 (15), 196 (15), 194 (99), 167 (13), 166 (11), 140 (18), 114 (13) and 98 (7).

3-(3-Formyl-indol-1-yl)-acrylic acid methyl ester 319.



Indole 3-carbaldehyde (82.5 mg, 0.57 mmol) and propynoic acid methyl ester (48 mg, 0.57 mmol) were dissolved in tetrahydrofuran (3 cm^3) and tetrabutylammonium fluoride (0.6 cm^3 of 1 M solution in tetrahydrofuran, 0.6 mmol) added dropwise with stirring. An immediate change from colourless to dark brown was observed the reaction was allowed to stir at room temperature for only 10 min. Tetrahydrofuran was removed *in vacuo* and the crude product purified by dry flash chromatography on silica (8% DCM, 20% ethyl acetate in hexane) to give *trans-3-(3-formylindol-1-yl)-acrylic acid methyl ester* **319** as a white solid (111 mg, 86%) mp 176-178 °C; (Found: M^+ 229.0737. $C_{13}H_{11}N_2O_3$ requires *M* 229.0739); δ_H 10.04 (1H, s), 8.21 (1H, d, ^3J 7.8), 8.16 (1H, d, ^3J 14.4), 8.00 (1H, s), 7.54 (1H, d, ^3J 7.8), 7.33 (2H, dq, ^3J 14.4 and 7.3), 6.17 (1H, d, ^3J 14.4) and 3.77 (3H, s); δ_C 184.48, 165.88 (quat), 136.09 (quat), 135.57, 132.69, 124.95, 123.83, 121.78, 121.49 (quat), 109.54, 104.24 and 51.12 (CH_3) (one quaternary overlapping); *m/z* 229 (M^+, 100%), 228 (70) 198 (25), 185 (17), 170 (58), 140 (13), 116 (16), 115 (31) and 98 (14).

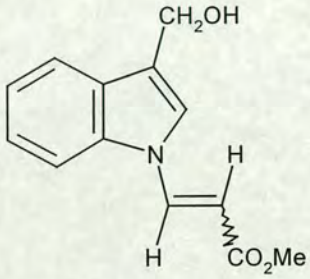
3-(3-Methyl-indol-1-yl)-acrylic acid methyl ester 320.



3-Methylindole (65.5 mg, 0.5 mmol) and propynoic acid methyl ester (42 mg, 0.5 mmol) were dissolved in tetrahydrofuran (3 cm^3) and tetrabutylammonium fluoride (0.5 cm^3 of 1 M solution in tetrahydrofuran, 0.5 mmol) added dropwise with stirring. The reaction was allowed to stir at room temperature for 30 min. Water (20 cm^3) was added and the organic components were extracted into ethyl acetate (3 × 40 cm^3). The crude products were absorbed onto silica and purified by dry flash chromatography on silica (20% DCM, 2% ethyl acetate in hexane) to give *3-(3-methylindol-1-yl)-acrylic acid methyl ester* **320** as a white solid (93 mg, 87%), mp 81-82 °C (from hexane), bp 169 °C (1.2 Torr); (Found: M^+ 215.0946. $C_{13}H_{13}NO_2$ requires *M* 215.0946); δ_H 8.14 (1H, d, ^3J 13.9), 7.43 (1H, d,

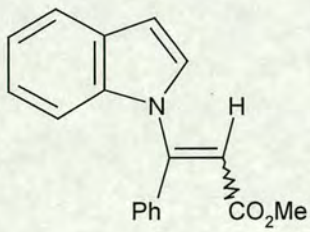
^3J 7.8), 7.26-7.10 (3H, m), 7.03 (1H, s), 5.73 (1H, dd, ^3J 13.9 and ^5J 0.9), 3.71 (3H, s) and 2.22 (3H, s); δ_C 167.52 (quat), 136.43, 135.77 (quat), 129.95 (quat), 123.32, 121.47, 119.93, 118.84, 117.97 (quat), 109.19, 97.86, 50.80 (CH_3) and 9.12 (CH_3); *m/z* 215 (M^+, 57%), 184 (47) 154 (17), 131 (81), 130 (100), 103 (23) and 77 (34).

Attempted synthesis of 3-(3-hydroxymethylindol-1-yl)-acrylic acid methyl ester 321.



Indole-3-methanol (147 mg, 1 mmol) and methyl propiolate (84 mg, 1 mmol) were added together in tetrahydrofuran (3 cm^3) and tetrabutylammonium fluoride (1 cm^3 of 1 M solution in tetrahydrofuran, 1 mmol) added dropwise with stirring. The reaction was allowed to stir at room temperature for 30 min. Water (20 cm^3) was added and the organic components extracted into ethyl acetate (3 × 40 cm^3). T.L.C. analysis showed four major components in the reaction mixture and its proton NMR spectrum indicated only trace quantities of the desired product so the synthesis was abandoned.

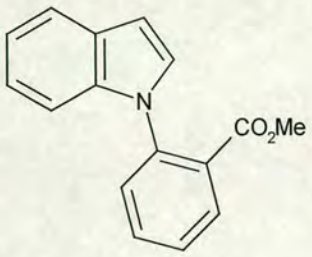
Attempted synthesis of 3-(indol-1-yl)-3-phenylacrylic acid methyl ester 322.



To a stirred solution of indole (58.5 mg, 0.5 mmol) and phenylpropynoic acid methyl ester (80 mg, 0.5 mmol) in tetrahydrofuran (3 cm^3) was added, dropwise, tetrabutylammonium fluoride (0.5 cm^3 of 1 M solution in tetrahydrofuran, 0.5 mmol). Proton NMR spectroscopy indicated no reaction had occurred after 4 h at room temperature and heating at reflux also failed to give any product.

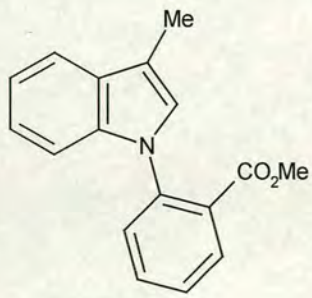
3.5.2 Synthesis of isoindoloindol-6-one precursors

2-(Indol-1-yl)-benzoic acid methyl ester 323.



A suspension of indole (2.93 g, 25 mmol), *o*-iodobenzoic acid (5.70 g, 23 mmol) and anhydrous potassium carbonate (6.91 g, 50 mmol) in dimethylformamide (50 cm^3) was heated under reflux, with stirring, for 48 h to give 2-(indol-1-yl)-benzoic acid **324**. The product was not isolated but treated with methyl iodide (3.55 g, 25 mmol) and anhydrous potassium carbonate (6.91 g, 50 mmol) and the reaction left to stir at room temperature for 48 h. Upon completion of the reaction water (120 cm^3) was added and the product extracted into ether (3 × 40 cm^3), washed with water (3 × 50 cm^3) and dried over anhydrous $MgSO_4$. Purification was achieved by distilling the crude product using a Kugelrohr oven under reduced pressure to give 2-(indol-1-yl)-benzoic acid methyl ester **323** (2.18 g, 35%) bp 108-110 °C (0.4 Torr) [no lit. bp reported]; δ_H 8.02 (1H, d, ^3J 8.2), 7.74-7.62 (2H, m), 7.55-7.47 (2H, m), 7.25-7.12 (4H, m), 6.71 (1H, d, ^3J 3.1), 3.48 (3H, s); δ_C 166.58 (quat), 138.49 (quat), 137.03 (quat), 132.61, 131.09, 128.70, 128.44 (2C, quat), 128.27, 127.42, 122.09, 120.77, 119.94, 109.58, 103.04 and 52.05; *m/z* 262 (M^+, 75%), 252 (41), 251 (95), 232 (24), 231 (80), 229 (36), 228 (26), 220 (41), 203 (50), 191 (47) and 117 (100) (spectra compatible with authentic data).[117]

2-(3-Methylindol-1-yl)-benzoic acid methyl ester 325.

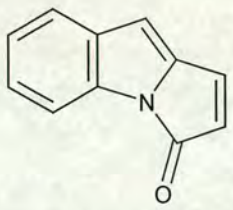


3-Methylindole (3.28 g, 25 mmol) was reacted under the conditions above to give *2-(3-methylindol-1-yl)-benzoic acid methyl ester* **325** (4.74 g, 72%) mp 96-98 °C, bp 103-104 °C (1 Torr); (Found: M^+ 265.1102. $C_{17}H_{15}NO_2$ requires *M* 265.1094); δ_H 7.85 (1H, m), 7.53-7.49 (2H, m), 7.39-7.33 (2H, m), 7.08-7.03 (3H, m), 6.90 (1H, m), 3.37 (3H, s) and 2.29 (3H, d, ^4J 1.1); δ_C 166.93 (quat), 138.73 (quat), 137.22 (quat), 132.55, 131.01, 128.54 (quat), 128.07, 126.95, 126.19, 122.12, 119.39, 118.91, 112.42 (quat), 109.49, 52.07 (CH_3) and 9.49

(CH_3) (one quaternary signal overlapping); *m/z* 265 (M^+, 100%), 264 (71), 263 (31), 262 (82), 250 (40), 232 (54), 231 (89), 204 (72) and 203 (63).

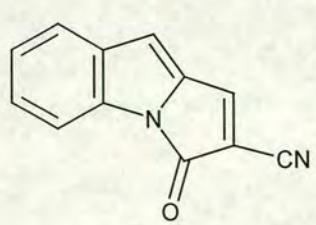
3.5.3 Synthesis of benzopyrrolizin-3-ones by flash vacuum pyrolysis

3*H*-Pyrrolo[1,2-*a*]indol-3-one 2.



Pyrolysis of 3-(3*H*-indol-3-yl)-acrylic acid methyl ester (100 mg, 0.5 mmol, T_i 210 °C, T_f 925 °C, P_{range} 0.01-0.09 Torr, *t* 25 min) afforded a solid yellow pyrolysate (71 mg, crude 85%) and subsequent purification by dry flash chromatography on silica (40% DCM in hexane) gave 3*H*-pyrrolo[1,2-*a*]indol-3-one **2** (59 mg, 70%)[31,19] mp 86-88 °C (lit.,[31] 86-89 °C); δ_H 7.60 (1H, ddd, ^3J 7.7, 1.7 and ^4J 0.9), 7.26 (1H, dt, ^3J 7.7 and ^4J 0.9), 7.15 (1H, td, ^3J 7.7 and ^4J 1.1), 7.02 (1H, d, ^3J 5.8), 6.94 (1H, td, ^3J 7.7 and ^4J 1.1), 6.27 (1H, s) and 5.88 (1H, d, ^3J 5.8) (spectral compatible with authentic data). However, large-scale pyrolysis (~500 mg) was found to be impractical due to the involatility of the precursor. The increase of inlet temperature required (up to 270 °C) to volatilise the precursor led to thermal degradation of the precursor and the formation of a white insoluble polymeric material as a side-product during the pyrolysis. Also apparent was the thermal degradation of the product during the course of the pyrolysis. Pyrolysis at a lower inlet temperature (210 °C) over a longer time period (~1.5 h) and the use of a 'cold-finger' trap to keep the pyrolysate cold did not significantly increase yields of 3*H*-pyrrolo[1,2-*a*]indol-3-one **2**. For these reasons the use of 3-(3*H*-indol-3-yl)-acrylic acid methyl ester **298** as a precursor for 3*H*-pyrrolo[1,2-*a*]indol-3-one **2** synthesis is not recommended.

2-Cyano-3*H*-pyrrolo[1,2-*a*]indol-3-one 326.



Pyrolysis of 2-cyano-3-(1*H*-indol-3-yl)-acrylic acid methyl ester **299** (302 mg, 1.3 mmol, T_f 925 °C, T_i 240 °C, P_{range} 0.02-0.10 Torr, *t* 20 min) using a dry ice/acetone cold-finger trap gave a solid orange pyrolysate of *2-cyano-3H-pyrrolo[1,2-a]indol-3-one*

326 that was purified by dry flash chromatography on silica (45% DCM and 1% ethyl acetate in hexane) (170 mg, 65%) mp 165-167 °C; (Found: M^+ 194.0478. $C_{12}H_6N_2O$ requires *M* 194.0480); δ_H 7.71 (1H, dt, ^3J 7.9 and ^4J 0.9), 7.70 (1H, s), 7.46 (1H, dt, ^3J 7.9 and ^4J 0.9), 7.39 (1H, td, ^3J 7.8 and ^4J 1.1), 7.16 (1H, td, ^3J 7.8 and ^4J 1.1) and 6.79 (1H, s); δ_C 158.65 (quat), 142.93, 137.42 (quat), 135.27 (quat), 133.54 (quat), 129.98, 124.51, 124.10, 115.28, 113.00, 111.62 (quat) and 111.18 (quat); *m/z* 194 (M^+, 100%), 166 (21), 165 (11), 140 (8) and 139 (26).

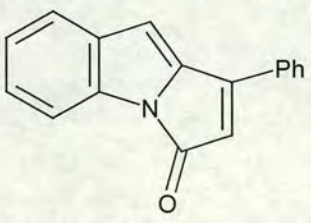
FVP of 2-(1*H*-indol-3-ylmethylene)-malonic acid dimethyl ester 300.

Pyrolysis (40 mg, 0.15 mmol, T_f 925 °C, T_i 210 °C, P_{range} 0.04-0.05 Torr, *t* 12 min) gave a yellow/brown oil pyrolysate. Proton NMR spectroscopic analysis indicated some 3*H*-pyrrolo[1,2-*a*]indol-3-one **2** was present [characteristic signals: 6.27 (1H, s) and 5.86 (1H, d, ^3J 5.8)] but that the major components of the pyrolysate were decomposition products. No further attempts at pyrolysis were made.

FVP of 3-(2-methyl-1*H*-indol-3-yl)-acrylic acid methyl ester 312.

Pyrolyses (30 mg, 0.22 mmol, T_i 210 °C, P_{range} 0.04-0.09 Torr, *t* 9 min) were performed at furnace temperatures of 800, 850, 900 and 925 °C. Full conversion of substrate required a furnace temperature of 925 °C and gave a yellow/brown solid pyrolysate. Proton NMR spectroscopic analysis indicated a trace of 9-methyl-3*H*-pyrrolo[1,2-*a*]indol-3-one **78** was present [characteristic signals: 5.81 (1H, d, ^3J 5.9) and 2.19 (3H, s)] but that the major components of the pyrolysate were decomposition products. No further attempts at pyrolysis were made

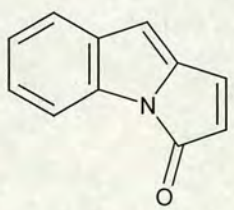
FVP of 3-(1*H*-indol-3-yl)-3-phenylacrylic acid methyl ester 302.



Pyrolysis (120 mg, 0.14 mmol, T_f 925 °C, T_i 210 °C, P_{range} 0.02-0.10 Torr, *t* 8 min) using a dry ice/acetone cold-finger trap gave a solid yellow pyrolysate that was washed into acetone and analysed by T. L. C. indicating two products (99 mg, 94%). Separation by dry flash chromatography (30% DCM and 1% ethyl acetate in hexane for the first band and 80% ethyl acetate for the second band) gave the following compounds in order of

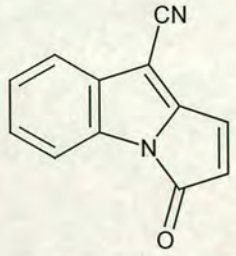
elution: *1-phenyl-3H-pyrrolo[1,2-a]indol-3one* **328** (60 mg, 57%) mp 111-113 °C; (Found: M^+ 245.0841. $C_{17}H_{11}NO$ requires *M* 245.0847); δ_H 7.68-7.62 (3H, m), 7.43-7.41 (3H, m), 7.37 (1H, dt, ^3J 7.8 and ^4J 0.8), 7.22 (1H, td, ^3J 7.6 and ^4J 1.1), 7.03 (1H, td, ^3J 7.6 and ^4J 1.1), 6.64 (1H, s) and 6.08 (1H, s); δ_C 164.82 (quat), 149.15 (quat), 140.27 (quat), 134.27 (quat), 130.79, 129.00 (2CH), 127.42, 127.00 (2CH), 123.05, 122.71, 119.87, 112.40 and 108.78 (one quaternary signal overlapping); *m/z* 245 (M^+, 100%), 217 (85), 216 (31), 204 (15), 189 (16), 149 (16), 123 (16), 109 (24), 95 (32) and 87 (94): *1-phenyl-4H-cyclopenta[b]indol-3-one* **333** or *3-phenyl-4H-cyclopenta[b]indol-1-one* **334** (6 mg, 6%) (not identified due to decomposition of the sample in solution during NOESY NMR experiment) mp 253-255 °C with decomposition; (Found: M^+ 245.0837. $C_{17}H_{11}NO$ requires *M* 245.0841); δ_H 11.44 (1H, br, s, NH), 8.02 (1H, dd, ^3J 7.6 and ^4J 0.6), 7.70-7.64 (4H, m), 7.47-7.41 (4H, m) and 6.59 (1H, s); δ_C 185.25 (quat), 147.85 (quat), 136.79 (quat), 135.39 (quat), 126.18 (quat), 111.02 (quat), 130.34, 128.75, 128.55 (2CH), 127.68 (2CH), 124.96, 124.16, 120.34 and 116.60 (one quaternary signal overlapping); *m/z* 245 (M^+, 100%), 244 (26), 217 (32), 216 (16), 189 (20), 169 (6) and 123 (9).

3*H*-Pyrrolo[1,2-*a*]indol-3-one 2.



Small scale pyrolyses of *3-(indol-1-yl)-acrylic acid methyl ester* **314** (25 mg, 0.12 mmol, T_i 90 °C, P_{range} 0.01-0.03 Torr, *t* 7 min) were performed at furnace temperatures of 900, 925 and 950 °C. The optimum temperature for full conversion to products was 925 °C. A preparative pyrolysis (300 mg, 1.5 mmol, T_i 90 °C, T_f 925 °C, P_{range} 0.01-0.08 Torr, *t* 40 min) afforded a solid yellow pyrolysate (230 mg, crude 90%) and subsequent purification by dry flash chromatography on silica (40% DCM in hexane) gave 3*H*-pyrrolo[1,2-*a*]indol-3-one **2** (200 mg, 78%)[31,19] mp 86-88 °C [lit.,[31] 86-89 °C]; δ_H 7.58 (1H, ddd, ^3J 7.7, 1.7 and ^4J 0.9), 7.27 (1H, dt, ^3J 7.7 and ^4J 0.9), 7.15 (1H, td, ^3J 7.7 and ^4J 1.1), 7.02 (1H, d, ^3J 5.8), 6.96 (1H, td, ^3J 7.7 and ^4J 1.1), 6.27 (1H, s) and 5.86 (1H, d, ^3J 5.8); δ_C 164.80 (quat), 141.17 (quat), 134.94, 134.44 (quat), 133.66 (quat), 127.31 (2C), 123.07, 122.72, 112.14 and 108.15 ; *m/z* 169 (M^+, 100%), 141 (47), 140 (37), 114 (26), 113 (16), 88 (12), 70 (13) and 63 (20).

9-Cyano-3*H*-pyrrolo[1,2-*a*]indol-3-one 338.

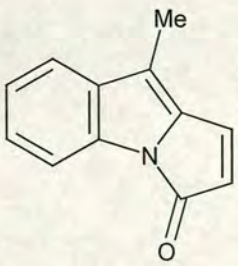


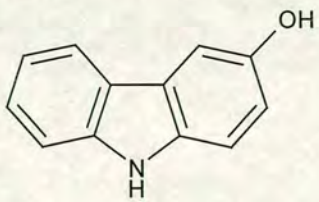
Pyrolysis of 3-(3-cyanoindol-1-yl)-acrylic acid methyl ester **318** (51 mg, 0.26 mmol, T_f 925 °C, T_i 165 °C, P_{range} 0.04-0.10 Torr, t 12 min) using a dry ice/acetone cold-finger trap gave a solid orange pyrolysate that was purified by dry flash chromatography (10% DCM and 10% ethyl acetate in hexane) to afford *9-cyano-3H-pyrrolo[1,2-a]indol-3-one* **338** (31 mg, 70%) mp 229-231 °C; (Found: M^+ 194.0478. $C_{12}H_6N_2O$ requires M 194.0480); δ_H 7.66 (1H, d, ^3J 7.9 and ^4J 0.8), 7.50 (1H, d, ^3J 7.9 and ^4J 0.8), 7.33 (1H, dt, ^3J 7.5 and ^4J 1.1), 7.30 (1H, d, ^3J 6.0), 7.18 (1H, dt, ^3J 7.5 and ^4J 1.1) and 6.14 (1H, d, ^3J 6.0); δ_C 164.74 (quat), 146.65 (quat), 134.77 (quat), 134.51 (quat), 133.27, 132.80 (quat), 131.16 (quat), 129.81, 129.50, 125.03, 121.93 and 113.28; *m/z* 194 (M^+, 69%), 168 (26), 167 (24), 166 (73), 142 (100), 139 (43), 115 (56) and 114 (30).

FVP of 3-(3-formylindol-1-yl)-acrylic acid methyl ester 319.

Pyrolysis (40 mg, 0.17 mmol, T_f 925 °C, T_i 205 °C, P_{range} 0.02-0.12 Torr, t 10 min) using a dry ice/acetone cold-finger trap gave a solid yellow pyrolysate. The pyrolysate was removed from the cold-finger by dissolving in acetone. The acetone was removed *in vacuo* after which NMR spectroscopy indicated the pyrolysate to be exclusively 3*H*-pyrrolo[1,2-*a*]indol-3-one **2** resulting from the loss of the formyl moiety *via* decarbonylation (32 mg, 94%); mp 86-88 °C (lit.,[31] 86-89 °C); δ_H 7.59 (1H, ddd, ^3J 7.7, 1.7 and ^4J 0.9), 7.29 (1H, dt, ^3J 7.7 and ^4J 0.9), 7.15 (1H, td, ^3J 7.7 and ^4J 1.2), 7.01 (1H, d, ^3J 5.8), 6.96 (1H, td, ^3J 7.7 and ^4J 1.2), 6.28 (1H, s) and 5.86 (1H, d, ^3J 5.8) (spectral data compatible with authentic data).

FVP of 3-(3-methylindol-1-yl)-acrylic acid methyl ester 320.



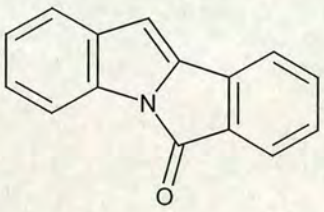


Pyrolysis (95 mg, 4.4 mmol, T_f 925 °C, T_i 160 °C, P_{range} 0.02-0.10 Torr, t 13 min) using a dry ice/acetone cold-finger trap gave a solid yellow pyrolysate

that was found to contain two major products by T. L. C. (isolated products 74 mg, 91%). Separation by dry flash chromatography (5-30% ethyl acetate in hexane gradient) gave the following compounds in order of elution: 9-methyl-3*H*-pyrrolo[1,2-*a*]indol-3-one **78** (36 mg, 53%) mp 92-93 °C [lit.,[19] 94-95 °C]; δ_H 7.58 (1H, d, ^3J 7.8), 7.24-7.20 (2H, m), 7.08 (1H, d, ^3J 5.9), 7.02 (1H, d, ^3J 78), 5.81 (1H, d, ^3J 5.9) and 2.19 (3H, s) (compatible with literature data): 9*H*-carbazol-3-ol **341** (32 mg, 47%)[118] mp 260-261 °C [lit.,[118] 259-260 °C]; δ_H 10.80 (1H, br, s), 8.85 (1H, br, s), 7.90 (1H, d, ^3J 7.8), 7.36 (1H, d, ^3J 7.8), 7.34 (1H, d, ^3J 8.4), 7.24 (1H, dt, ^3J 7.4, ^4J 1.1), 7.22 (1H, d, ^3J 8.4), 6.99 (1H, dt, ^3J 7.4, ^4J 1.1) and 6.83 (1H, dd, ^3J 8.6 and 2.4); *m/z* 183 (M^+, 14%), 170 (7), 154 (8), 143 (28), 130 (14), 129 (100), 128 (21), 115 (8) and 102 (24). Pyrolysis of 9-methyl-3*H*-pyrrolo[1,2-*a*]indol-3-one **78** (20 mg, 0.11 mmol, T_f 925 °C, T_i 160 °C, P_{range} 0.02-0.05 Torr, *t* 9 min) gave a 50 : 50 mixture of 9-methyl-3*H*-pyrrolo[1,2-*a*]indol-3-one **78** and 9*H*-carbazol-3-ol **341** shown by proton NMR spectroscopy.

3.5.4 Synthesis of isoindoloindol-6-ones by flash vacuum pyrolysis

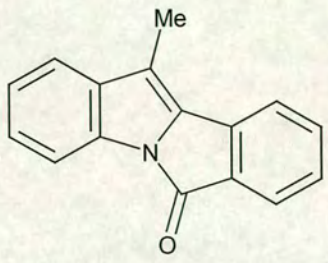
Isoindolo[2,1-*a*]indol-6-one 3.



Small scale pyrolyses of 2-(indol-1-yl)-benzoic acid methyl ester **323** (30 mg, 0.12 mmol, T_i 100 °C, P_{range} 0.02-0.10 Torr, *t* 10 min) at 900, 950 and 950 °C with silica tubes at furnace exit indicated that the optimum conversion of substrate was achieved at 950 °C with silica tubes at furnace exit. A preparative pyrolysis (400 mg, 1.6 mmol, T_f 950 °C with silica tubes T_i 100 °C, P_{range} 0.01-0.12 Torr, *t* 40 min) gave a solid yellow pyrolysate containing isoindolo[2,1-*a*]indol-6-one **3** that was purified by dry flash chromatography on silica (50% DCM in hexane as eluent) (220 mg, 76%) mp 153-154 °C [lit.,[33] 154-155 °C]; δ_H 7.76 (1H, dd, ^3J 7.9, ^4J 0.8), 7.66 (1H, dt, ^3J 7.5, ^4J 0.9), 7.44-7.41 (2H, m), 7.36 (1H, dt, ^3J 7.7, ^4J 1.1), 7.29-7.17 (2H, m), 7.03 (1H, td, ^3J 7.6, ^4J 1.0) and 6.52 (1H, s); δ_C 162.51 (quat), 138.69 (quat), 136.85 (quat), 134.51 (quat), 134.35 (quat), 133.71 (quat), 133.43, 128.51, 126.06, 124.97, 123.64, 122.05,

120.99, 113.06 and 103.26; *m/z* 219 (M^+, 100%), 191 (42), 190 (80), 164 (44), 163 (46), 110 (56), 96 (48) and 82 (56).

11-Methyl-isoindolo[2,1-*a*]indol-6-one 118.



Pyrolysis of 2-(3-methylindol-1-yl)-benzoic acid methyl ester **325** (265 mg, 1.0 mmol, T_f 950 °C with silica tubes T_i 120 °C, P_{range} 0.01-0.11 Torr, *t* 40 min) using a dry ice /acetone cold-finger trap gave a solid yellow pyrolysate containing 11-methyl-isoindolo[2,1-a]indol-6-one **118** that was purified by dry flash chromatography on silica (20-50% DCM in hexane as eluent) to afford yellow needles (121 mg, 72%)[34] mp 173-174 °C [lit.,[37] 174-175 °C], bp 177 °C (4.5 Torr); δ_H 7.75 (1H, dt, ^3J 7.9, ^4J 0.8), 7.63 (1H, d, ^3J 7.5, ^4J 1.0), 7.42 (1H, m), 7.38 (1H, td, ^3J 7.5, ^4J 1.0), 7.26 (1H, m), 7.22-7.14 (2H, m), 7.05 (1H, td, ^3J 7.5, ^4J 1.0) and 2.37 (3H, s); δ_C 164.16 (quat), 135.64 (quat), 134.89 (quat), 133.42 (quat), 133.31, 127.92, 126.37, 125.16, 123.77 (quat), 123.46, 121.13 (quat), 121.01, 120.05, 115.26 (quat), 113.16 and 9.36 (CH_3); *m/z* 233 (M^+, 99%), 232 (77), 219 (100), 204 (59), 203 (79) and 102 (34).

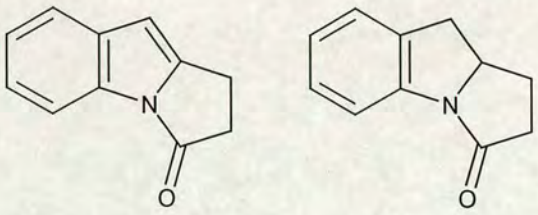
3.6 Hydrogenation reactions

3.6.1 Hydrogenation at medium pressures

General method

All hydrogenation reactions were performed using Parr 3921 apparatus at room temperature and at medium pressure (40-60 PSI). Hydrogenations were performed as follows: substrate (30-50 mg) was dissolved in solvent (15-25 cm^3) and hydrogenated with a heterogeneous catalyst (~5 mg) over a recorded time interval. Catalyst was removed from the completed reaction by filtration through a celite pad and removal of the solvent afforded the crude hydrogenation products.

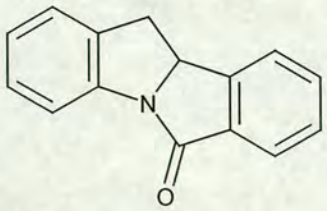
Hydrogenation of pyrrolo[1,2-*a*]indol-3-one 2.



A solution of pyrrolo[1,2-*a*]indol-3-one **2** (30 mg, 0.18 mmol) in toluene (25 cm^3) was hydrogenated at 40 PSI over 5% Pd-C (5 mg) for 2 h during which time the solution decolourised. Filtration through celite and concentration by rotary evaporator gave 1,2-dihydropyrrolo[1,2-*a*]indol-3-one **96** as a colourless solid (29 mg, 97%)[31] mp 150-152 °C [lit.,[31] 153-154 °C]; δ_H 7.99 (1H, m), 7.42 (1H, m), 7.22-7.16 (2H, m), 6.19 (1H, d, ^4J 0.6) and 3.08-2.96 (4H, m); δ_C 171.56 (quat), 143.48 (quat), 135.15 (quat), 130.23 (quat), 123.87, 123.05, 120.36, 113.41, 100.19, 34.66 (CH_2) and 19.44 (CH_2); *m/z* 171 (M^+, 95%), 143 (85), 129 (74), 115 (64), 97 (70), 83 (72), 71 (85), 55 (94) and 43 (100). Proton NMR spectroscopy also indicated traces of *1,2,9,9a-tetrahydropyrrolo[1,2-a]indol-3-one* **347** were present (8%) (see experimental section 3.8.2).

Two further hydrogenations at 60 PSI with 5% Pd-C and 5% Rh-C did not increase the proportion of *1,2,9,9a-tetrahydropyrrolo[1,2-a]indol-3-one* **347** in the reaction mixture.

10*b*,11-Dihydroisoindolo[2,1-a]indol-6-one 348.

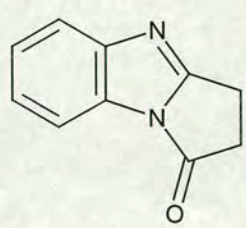


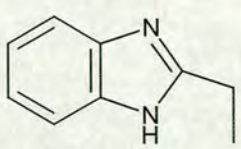
A solution of isoindolo[2,1-*a*]indol-6-one **3** (51 mg, 0.23 mmol) in ethanol (25 cm^3) was hydrogenated at 40 PSI over 5% Pd-C (5 mg) for 6 h during which time the solution decolourised. Filtration through celite and concentration by rotary evaporator gave *10b,11-dihydroisoindolo[2,1-a]indol-6-one* **348** as a colourless solid (50 mg, 98%) mp 127-129 °C; (Found: M^+ 221.0840. $C_{15}H_{11}NO$ requires *M* 221.0841); δ_H 7.80 (1H, m), 7.60 (1H, d, ^3J 7.8), 7.52 (1H, m), 7.44-7.38 (2H, m), 7.27-7.13 (2H, m), 6.98 (1H, t, ^3J 7.5), 5.52 (1H, t, ^3J 9.5), 3.37 (1H, dd, ^3J 15.2 and 8.7) and 2.95 (1H, dd, ^3J 15.0 and 10.4); δ_C 168.25 (quat), 145.87 (quat), 140.43 (quat), 135.82 (quat), 134.01 (quat), 132.42, 128.56, 127.83, 125.21, 124.66, 124.30, 122.70, 116.31, 65.29 and 33.61 (CH_2); *m/z* 221 (M^+, 86%), 220 (89), 219 (77), 193 (81), 192 (64), 191 (80), 190 (62), 165 (71), 130 (52), 105 (53) and 95 (100).

Hydrogenation of 11-methylisoindolo[2,1-*a*]indol-6-one 118.

A solution of 11-methylisoindolo[2,1-*a*]indol-6-one **118** (43 mg, 0.18 mmol) in ethanol (25 cm^3) was hydrogenated at 40 PSI over 5% Pd-C (5 mg) for 8 h. Proton NMR spectroscopy indicated no hydrogenation had occurred. Further hydrogenation at 60 PSI over 5% Rh-C for 8 h returned starting material with a trace of *10b,11-dihydro-11-methylisoindolo[2,1-a]indol-6-one* **349**.

Hydrogenation of pyrrolo[1,2-*a*]benzimidazol-1-one 280.





A solution of pyrrolo[1,2-*a*]benzimidazol-1-one **280** (25 mg, 0.15 mmol) in toluene (25 cm^3) was hydrogenated at 45 PSI over 5% Pd-C (5 mg) for 2 h. Filtration through celite and concentration by rotary evaporator afforded the crude hydrogenation products (21.7 mg, *ca.* 86% total). Two products were identified in a 50 : 50 mixture by proton NMR spectroscopy: 2,3-dihydrobenzo[*d*]pyrrolo[1,2-

a]imidazol-1-one **350** δ_H 7.86 (1H, m), 7.64 (1H, m), 7.33-7.27 (2H, m) and 3.26-3.12 (4H, m); δ_C 169.74 (quat), 161.94 (quat), 149.10 (quat), 128.37 (quat), 125.40, 124.29, 119.86, 112.99, 34.40 (CH_2) and 21.04 (CH_2) (in agreement with literature data[119]); *m/z* 172 (M^+, 85%); and 2-ethylbenzimidazole **351** [identified by comparison with an authentic sample made as follows: 1,2-phenylenediamine (0.43 g) and propionic acid (0.33 g) were heated under reflux for 1 h. The hot solution was diluted with cold water (15 cm^3) and basified with 1M NaOH. The aqueous layer was extracted with DCM (3 × 30 cm^3), dried over $MgSO_4$, filtered and concentrated by rotary evaporator to give 2-ethylbenzimidazole **351** (0.44 g, 75%) mp 172-174 °C [lit.,[120] 166-168 °C]; δ_H 7.46 (2H, dd, ^3J 6.1 and 3.2), 7.12 (2H, dd, ^3J 6.1 and 3.2), 2.91 (2H, q, ^3J 7.7) and 1.34 (2H, t, ^3J 7.6); δ_C 156.50 (quat), 138.24 (2 quat), 121.96 (2CH), 114.39 (2CH), 22.37 (CH_2) and 12.31 (CH_3); *m/z* 146 (M^+, 64%), 145 (100), 131 (25), 118 (10), 63 (12) and 39 (12)].

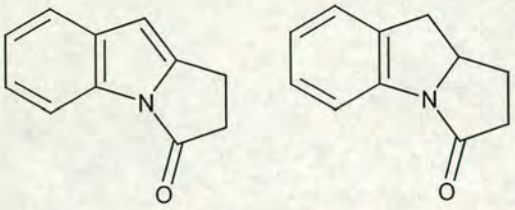
Another hydrogenation under the same conditions over 30 min also yielded both products indicating that selective reduction to the 2,3-dihydro product over the ring-opened product is unobtainable *via* this route.

3.6.2 Hydrogenations at high pressure

General method

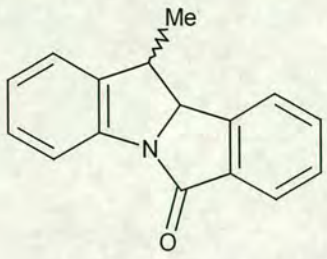
All reactions were performed using Parr 4842 hydrogenation apparatus at high pressure (300-1100 PSI) and at temperatures between 20-50 °C. Hydrogenations were performed as follows: substrate was dissolved in solvent and transferred to the reaction vessel then hydrogenated with a heterogeneous catalyst (~5 mg) over a recorded time interval. Filtration through a celite pad and removal of the solvent afforded the crude hydrogenation products.

Hydrogenation of pyrrolo[1,2-*a*]indol-3-one 2.



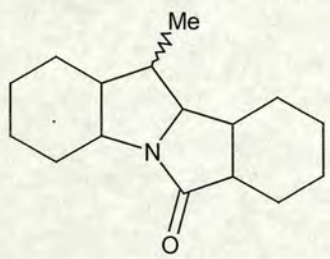
Initial hydrogenation reactions of pyrrolo[1,2-*a*]indol-3-one **2** (30 mg, 0.18 mmol) were performed in toluene at temperatures between 20-60 °C and at pressures up to 600 PSI using 5% Pd-C or 5% Rh-C. The largest degree of hydrogenation reached under these conditions was an apparent equilibrium mixture (90 : 10) of 1,2-dihydro and 1,2,9,9a-tetrahydro products. However, when a 10 : 1 mixture of ethanol and acetic acid as solvent (25 cm^3) and 5% Rh-Al_2O_3 (5 mg) as catalyst was used at room temperature to hydrogenate pyrrolo[1,2-*a*]indol-3-one **2** (30 mg, 0.18 mmol) at a pressure of 400 PSI over a 5 h period a proton NMR spectrum showed the hydrogenation mixture to contain an approximately 1 : 1 mixture of 1,2-dihydro and 1,2,9,9a-tetrahydro products with traces of aromatic hydrogenation products. Separation by dry flash chromatography using 2-30% ethyl acetate in hexane as eluent yielded 1,2-dihydropyrrolo[1,2-*a*]indol-3-one **96** (14 mg, 46%) (spectrum as above) and *1,2,9,9a-tetrahydropyrrolo[1,2-a]indol-3-one* **347** (13 mg, 42%) mp 134-136 °C; (Found: M^+ 173.0840. $C_{11}H_{11}NO$ requires *M* 173.0841); δ_H 7.53 (1H, d, ^3J 7.8), 7.19-7.09 (2H, m), 6.95 (1H, td, ^3J 7.6, ^4J 1.0), 4.64-4.50 (1H, m), 3.10 (1H, dd, ^3J 15.7 and 7.2), 2.88-2.76 (2H, m), 2.51 (1H, ddd, ^3J 16.6 and 8.4, ^4J 0.8), 2.41 (1H, m) and 1.92 (1H, m); δ_C 171.56 (quat), 139.01 (quat), 133.99 (quat), 127.52, 125.11, 123.99, 114.57, 62.83, 36.21 (CH_2), 35.65 (CH_2) and 29.22 (CH_2); *m/z* 173 (M^+, 83%), 144 (30), 130 (50), 119 (64), 118 (100), 117 (79), 91 (64), 90 (70) and 89 (77). A second hydrogenation, under the same conditions, over 8 h gave a mixture products ranging from *1,2,9,9a-tetrahydropyrrolo[1,2-a]indol-3-one* **347** (spectrum as above) to the fully saturated *decahydropyrrolo[1,2-a]indol-3-one* **352** tentatively identified by proton NMR signals between δ_H 1.1-2.7 corresponding to 17 aliphatic protons and a mass peak of *m/z* 179 in the mass spectrum (see discussion section 2.4.1.2). No separation of the hydrogenation mixture was performed.

Hydrogenation of 11-methylisoindolo[2,1-*a*]indol-6-one 118.



Solutions of 11-methylisoindolo[2,1-*a*]indol-6-one **118** (30 mg, 0.13 mmol) in toluene (25 cm^3) were hydrogenated at 600, 850, 1000 Bar and 1000 Bar with heating at 50 °C over 5% Pd-C, 10% Pd-C and 5% Rh-C for 6 h. No hydrogenation was observed. 11-Methylisoindolo[2,1-*a*]indol-6-one **118** (30 mg, 0.13 mmol) hydrogenated in 10 : 1 of mixture ethanol and acetic acid over 5% Rh-Al_2O_3 (5 mg) at room temperature and a pressure of 400 PSI for 3 h gave a mixture of hydrogenation products. T. L. C. analysis indicated three hydrogenation products and separation by dry flash chromatography using a 2-40% ethyl acetate in hexane gradient as eluent afforded three products. The major product was identified as 10b,11-dihydro-11-methylisoindolo[2,1-*a*]indol-6-one **349** (24 mg, 80%) and characterised by NMR spectroscopy only; δ_H 7.91 (1H, m), 7.71 (1H, dd, ^3J 7.8, ^4J 0.4), 7.62 (1H, td, ^3J 7.5, ^4J 1.3), 7.54-7.49 (2H, m), 7.35-7.26 (2H, m), 7.11 (1H, td, ^3J 7.5, ^4J 0.9), 5.53 (1H, d, ^3J 7.9), 3.62 (1H, quin, ^3J 14.8 and 7.4) and 0.76 (3H, d, ^3J 7.2); δ_C 168.00 (quat), 142.98 (quat), 141.65 (quat), 138.82 (quat), 134.98 (quat), 132.00, 128.52, 127.99, 124.77, 124.44 (2CH), 123.55, 116.22, 68.65, 37.73 and 18.22 (CH_3). The two other hydrogenation products were not fully characterised (see discussion section 2.4.1.2).

11-Methyl-tetradecahydro-isoindolo[2,1-*a*]indol-6-one 353.



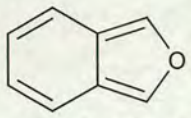
A hydrogenation of **118** (30 mg, 0.13 mmol)) at room temperature and a pressure of 400 PSI for 18 h at gave the fully saturated *11-Methyl-tetradecahydro-isoindolo[2,1-a]indol-6-one* **353** (see discussion section 2.4.1.2) (29 mg, 97%) (crude product not purified for melting point analysis); (Found: M^+ 247.1939. $C_{16}H_{25}NO$ requires *M* 247.1936); δ_H 3.82 (1H, dd, ^3J 7.6 and 4.6), 3.52 (1H, dd, ^3J 13.1 and 6.6), 2.63 (1H, t, ^3J 5.3), 2.42-2.27 (2H, m), 2.22-0.87 (17H, m), 1.11 (3H, d, ^3J 7.5); δ_C 152.52 (quat), 65.89, 52.98, 48.10, 42.60, 40.47, 37.54, 27.65 (CH_2), 25.44 (CH_2), 24.33 (CH_2), 24.11 (CH_2), 23.47 (CH_2), 23.08 (CH_2), 22.79

(CH_2), 22.07 (CH_2) and 14.08 (CH_3); *m/z* 247 (M^+, 86%), 204 (79), 190 (51), 152 (55), 138 (83), 95 (70), 81 (89), 67 (84) and 55 (100).

3.7 Pericyclic reactions

3.7.1 Diels-Alder reactions with isobenzofuran

Isobenzofuran 354.

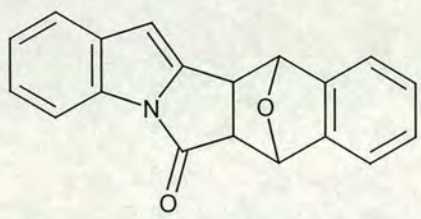


Flash vacuum pyrolysis of 1,4-epoxy-1,2,3,4-tetrahydronaphthalene **355** (32 mg, 0.2 mmol, T_f 650 °C, T_i 60 °C, 0.02 Torr, 5 min) was performed using a cold-finger trap maintained at –78 °C. The colourless crystals were washed from the trap under nitrogen using ice-cold acetone into a round bottomed flask. The flask was connected to a to an oil pump with liquid nitrogen trap and the solvent removed without heating to give isobenzofuran **354** as a white solid (25 mg, 97%);[94] δ_H 8.04 (2H, s), 7.48-7.36 (2H, m) and 6.91-6.81 (2H, m).

General method

Flash vacuum pyrolysis of 1,4-epoxy-1,2,3,4-tetrahydronaphthalene **355** gave isobenzofuran **354** as a white solid collected on a cold-finger at –78 °C in quantitative yield. The product was washed under nitrogen off the cold-finger with the minimum amount of ice-cold deuteriated acetone and added directly to an ice-cooled solution of (aza-)benzopyrrolizinone also in deuteriated acetone. The reaction mixture was warmed to room temperature during which time the colour faded. NMR spectra were performed allowing calculation of the cycloadduct *endo* : *exo* ratio (as described in the corresponding Section) before the solvent was removed under vacuum to give crystalline solid. Reaction time and *endo* : *exo* ratio are indicated.

8,13-Epoxy-7*a*,8,13,13*a*-tetrahydro-7*H*-benzo[*f*]indolo[2,1-*a*]isoindol-7-one 356.

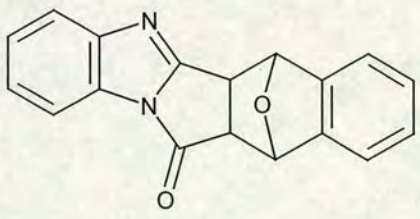


{From 3*H*-pyrrolo[1,2-*a*]indol-3-one **2** (34 mg, 0.2 mmol) in deuteriated acetone (1 cm^3) and 1,4-epoxy-1,2,3,4-tetrahydronaphthalene [(32 mg, 0.2 mmol), T_f 650 °C, T_i 60 °C, 0.02 Torr, 5min] 30 min, 100 : 0. } *endo* **356** (53 mg, 92%), mp 200-202 °C (Found: M^+ 287.0948. $C_{19}H_{13}NO_2$ requires

M 287.0946); δ_H 7.55 (1H, m), 7.28 (1H, m), 7.22 (1H, d, ^3J 7.1), 7.06-7.00 (2H, m), 6.92 (1H, t, ^3J 7.5 and ^4J 1.0), 6.90 (1H, d, ^3J 7.1), 6.77 (1H, t, ^3J 7.5 and ^4J 1.0), 6.12 (1H, s), 5.68 (1H, d, ^3J 5.3), 5.55 (1H, d, ^3J 5.3), 4.16 (1H, ddd, ^3J 8.1, 5.3 and ^4J 1.1) and 4.07 (1H, dd, ^3J 8.1, 5.3); δ_C 168.21 (quat), 140.91 (quat), 140.55 (quat), 140.50 (quat), 134.12 (quat), 129.69 (quat), 127.33 (2CH), 123.80, 123.50, 120.64, 120.47, 120.27, 113.05, 100.96, 81.52, 79.79, 55.51 and 40.74; *m/z* 287 (M^+, 51%), 259 (13), 230 (42), 228 (30), 202 (23), 169 (72), 148 (47), 140 (55), 133 (74), 119 (66) and 118 (100).

In a complementary experiment both 1,4-epoxy-1,2,3,4-tetrahydronaphthalene **355** (32 mg, 0.2 mmol), and *3-(1H-indol-1-yl)-acrylic acid methyl ester* **308** (34 mg, 0.2 mmol) were pyrolysed together (T_f 925 °C, T_i 115 °C, 0.02 Torr, 10 min) which resulted in formation of cycloadduct (*endo* : *exo* ratio 100 : 0) that was recrystallised from the minimum volume of isopropyl alcohol (37 mg, 64%). This process was not as efficient as the addition of isobenzofuran **354** to 3*H*-pyrrolo[1,2-*a*]indol-3-one **2** (see above) and may be due to reactions of isobenzofuran with ring-closure by-products such as methanol.

8,13-Epoxy-7*a*,8,13,13*a*-tetrahydro-7*H*-benzo[*f*]benzimidazo[2,1-*a*]isoindol-7-one 357.

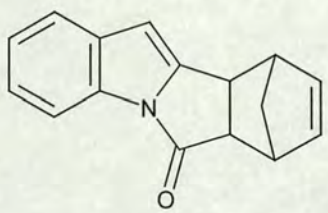


{From pyrrolo[1,2-*a*]benzimidazol-1-one **280** (47 mg, 2.8 mmol) in deuteriated acetone (1 cm^3) and 1,4-epoxy-1,2,3,4-tetrahydronaphthalene **355** (41 mg, 2.8 mmol) [T_f 650 °C, T_i 60 °C, 0.02 Torr, 7min] 5 min, 100 : 0.} *endo* **357** (60 mg, crude yield 75%). Isolation of the adduct proved to be very difficult as rapid degradation occurred whether attempting purification by recrystallisation from a variety of solvents or by dry flash column chromatography. A few small crystals were eventually obtained from a fortuitous recrystallisation from toluene in which the vast majority of the crude product was lost to degradation; mp 216-218 °C (Found: M^+ 288.0890 $C_{18}H_{12}N_2O_2$ requires *M* 288.0898); δ_H ([$^2H_6$]acetone) 7.40 (1H, ddd, ^3J 7.5, ^4J 1.4 and ^nJ 0.9), 7.31 (1H, ddd, ^3J 7.5, ^4J 1.4

and ^{n}J 0.9), 7.16 (1H, m), 7.12 (1H, td, ^{3}J 7.8 and ^{4}J 1.6), 7.04 (1H, td, ^{3}J 7.5 and ^{4}J 1.3), 6.90 (1H, m), 6.88 (1H, td, ^{3}J 7.4 and ^{4}J 1.1), 6.72 (1H, td, ^{3}J 7.4 and ^{4}J 1.0), 5.75 (1H, dd, ^{3}J 7.8, 5.7 and ^{4}J 1.8), 5.71 (1H, dd, ^{3}J 7.8, 5.7 and ^{4}J 1.8), and 4.29 (2H, m); δ_C 166.57 (quat), 158.91 (quat), 147.99 (quat), 140.99 (quat), 140.344 (quat), 126.82 (quat), 126.49, 126.39, 124.01, 123.22, 119.79, 119.58, 118.98, 111.25, 79.72, 78.68, 54.87 and 41.53; *m/z* 288 (M^+, 10%), 234 (14), 208 (14), 180 (100), 179 (84), 178 (95), 165 (78), 142 (68) and 119 (57).

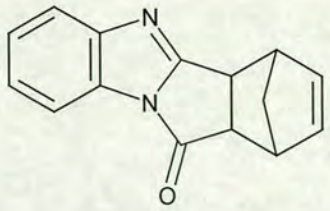
3.7.2 Diels-Alder reactions with cyclopentadiene

8,11-Methano-7*a*,8,11,11*a*-tetrahydro-7*H*-indolo[2,1-*a*]isoindol-7-one 360.



A solution of 3*H*-pyrrolo[1,2-*a*]indol-3-one **2** (100 mg, 0.59 mmol) in acetone (2 cm^3) was treated with freshly distilled cyclopentadiene **358** (41 mg, 0.62 mmol). The reaction mixture was left to stand for 1 h at room temperature during which time slight decolourisation occurred. Excess cyclopentadiene and the solvent were removed under vacuum and the crude product purified by hot filtration and recrystallisation from hexane to afford only the *endo* Diels-Alder cycloadduct **360** (determined from the proton NMR spectrum, as described in the discussion section) as colourless crystals (127 mg, 92%), mp 125-127 °C (Found: C, 81.45; H, 5.55; N, 5.9. $C_{16}H_{13}NO$ requires C, 81.7; H, 5.55; N, 5.95%); (Found: M^+ 235.0997 $C_{16}H_{13}NO$ requires *M* 235.0997); δ_H 7.90 (1H, m), 7.37 (1H, m), 7.18-7.11 (2H, m), 6.13 (1H, m), 5.99 (1H, dd, ^{3}J 5.7, 2.9), 5.73 (1H, dd, ^{3}J 5.7, 3.0), 3.69 (1H, ddd, ^{3}J 7.3, 4.3 and ^{4}J 1.2), 3.57 (1H, dd, ^{3}J 7.3 and 4.3), 3.34 (1H, dd, ^{3}J 2.5 and ^{4}J 1.2), 3.22 (1H, dd, ^{3}J 2.5 and ^{4}J 1.2), 1.71 (1H, dt, ^{3}J 8.7 and ^{4}J 1.8) and 1.56 (1H, m); δ_C 172.26 (quat), 144.83 (quat), 135.09, 134.83 (quat), 133.73, 129.83 (quat), 123.71, 123.07, 120.39, 113.52, 99.61, 53.53, 51.91 (CH_2), 45.96, 44.43 and 38.84; *m/z* 235 (M^+, 41%), 170 (54), 169 (100), 141 (50), 140 (45) and 114 (34).

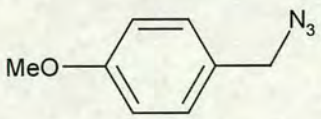
8,11-Methano-7*a*,8,11,11*a*-tetrahydro-7*H*-benzimidazo[2,1-*a*]isoindol-7-one 361.



A solution of pyrrolo[1,2-*a*]benzimidazol-1-one **280** (40 mg, 0.23 mmol) in deuteriated acetone (0.5 cm^3) was treated with a small excess of freshly distilled cyclopentadiene **358** (16 mg, 0.24 mmol) and the reaction followed by proton NMR spectroscopy. Decolourisation occurred over 5 min to afford only the *endo* Diels-Alder cycloadduct **361** (determined from the proton NMR spectrum, as described in the discussion section). The solvent and excess cyclopentadiene were removed under as mild conditions as possible using FVP apparatus [0.02 Torr] to prevent thermal degradation of the product, 8,11-Methano-7*a*,8,11,11*a*-tetrahydro-7*H*-benzimidazo[2,1-*a*]isoindol-7-one **361** (50 mg, 90%), mp 108-110 °C (Found: M^+ 236.0948. $C_{15}H_{12}N_2O$ requires *M* 236.0950); δ_H ([$^2H_6$]acetone) 7.61 (1H, m), 7.47 (1H, m), 7.20-7.14 (2H, m), 5.90 (1H, dd, ^3J 5.7, 2.9), 5.67 (1H, dd, ^3J 5.7, 2.9), 4.00-3.77 (2H, m), 3.32-3.22 (2H, m, br) and 1.64-1.59 (2H, m, br); δ_C 170.04 (quat), 162.17 (quat), 148.34 (quat), 134.10, 132.93, 127.10 (quat), 123.97, 122.98, 118.89, 111.64, 52.47, 51.26 (CH_2), 44.30, 43.65 and 39.32; *m/z* 236 (M^+, 58%), 207 (10), 171 (70), 170 (99), 142 (64), 118 (36), 115 (37), 102 (38), 91 (44) and 41 (100).

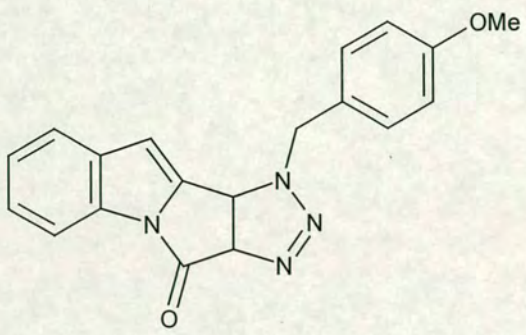
3.7.3 1,3-Dipolar cycloaddition reactions with azide

4-Methoxybenzyl azide 364.



Sodium azide (0.40 g, 6 mmol) was added to a solution of 4-methoxybenzyl bromide (0.96 g, 6 mmol) in DMF (10 cm^3) and the reaction left to stir for 24 h at room temperature. Water (100 cm^3) and diethyl ether (3 × 10 cm^3) were added and the organic extracts separated then dried over $MgSO_4$. Removal of the solvent at the lowest possible temperature afforded 4-methoxybenzyl azide **364** as a colourless oil (0.91 g, 93%)[121]; δ_H 7.23 (2H, d, ^3J 6.6), 6.90 (2H, d, ^3J 6.6), 4.26 (2H, s) and 3.81 (3H, s).

1-(4-Methoxybenzyl)-3a,10b-dihydro-[1,2,3]triazolo[4',5':3,4]pyrrolo[1,2-*a*]indol-4-one 365.

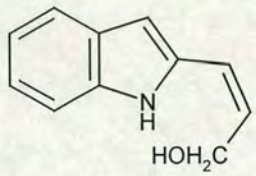


4-Methoxybenzyl azide **364** (196 mg, 1.2 mmol) was added dropwise to a stirred solution of 3*H*-pyrrolo[1,2-*a*]indol-3-one **2** (72 mg, 0.4 mmol) in acetone (5 cm^3) and heated at 75 °C for 24 h during which time a precipitate formed. The mixture was concentrated to ~1 cm^3 and cooled in a freezer overnight. The precipitated product was filtered and washed with ethyl acetate (10 drops) to give *1-(4-methoxybenzyl)-3a,10b-dihydro-[1,2,3]triazolo[4',5':3,4]pyrrolo[1,2-a]indol-4-one* **365** as white needles (103 mg, 72%) mp 192-194 °C (decomposition with gas evolution); (Found: C, 68.90; H, 5.10; N, 16.80. $C_{19}H_{16}N_4O_2$ requires C, 69.00; H, 4.80; N, 16.90); δ_H (DMSO) 7.91 (1H, m), 7.75 (1H, m), 7.64-7.61 (4H, m), 6.99 (2H, d, ^3J 8.4), 6.51 (1H, s), 5.93 (1H, d, ^3J 10.5), 5.04 (1H, d, ^3J 14.8), 4.98 (1H, d, ^3J 10.5), 4.79 (1H, d, ^3J 14.8) and 3.78 (3H, s); δ_C 164.83 (quat), 158.82 (quat), 140.51 (quat), 134.46 (quat), 129.75 (2CH), 129.63 (quat), 127.32 (quat), 124.43, 121.65, 113.90 (2CH), 112.94, 102.90, 87.72, 54.92, 52.08, 50.44 (CH_2) and 30.44 (CH_3); *m/z* (e.i.) 332 (M^+, 0.7%), 304 (42), 275 (6), 236 (9), 170 (13), 169 (27), 141 (23), 122 (43) and 121 (100); *m/z* (FAB) 333 (MH^+, 100%).

3.8 Reactions with nucleophiles

3.8.1 Ring opening reactions with lithium aluminium hydride

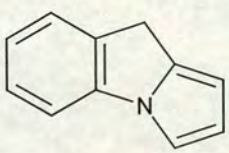
cis-3-(1*H*-Indol-2-yl)-prop-2-en-1-ol 367.



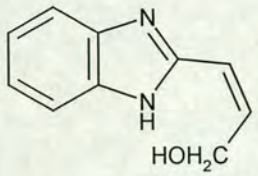
A solution of 3*H*-pyrrolo[1,2-*a*]indol-3-one **2** (26 mg, 0.15 mmol) in dry ether (10 cm^3) was added to a suspension of lithium aluminium hydride (23 mg, 0.60 mmol) in dry ether (10 cm^3) under a nitrogen atmosphere at such a rate as to produce gentle reflux. The solution was then heated under reflux for a further 30 min. After cooling in ice, wet ether (10 cm^3), water (10 cm^3) and an aqueous solution of potassium tartrate (20%, 5 cm^3) were added and the solution shaken vigorously then filtered through a pad of celite. The ether layer was separated and the aqueous phase extracted with ether (3 × 30 cm^3). The organic extracts were dried over $MgSO_4$, filtered and the ether removed by rotary evaporator to give *cis-3-(1H-indol-2-yl)-prop-2-en-1-ol* **367** (27 mg, 99%) mp 103-104 °C; (Found: M^+ 173.0841. $C_{11}H_{11}NO$ requires *M* 173.0841); δ_H 9.64 (1H, br s, NH), 7.51 (1H, dd, ^3J 7.2, ^4J 0.8), 7.28 (1H, dd, ^3J 7.2, ^4J 0.8), 7.10 (1H, td, ^3J 7.0, ^4J 1.2), 7.00 (1H, td, ^3J 7.0, ^4J 1.2), 6.54 (1H, d, ^3J 12.0), 6.40 (1H, s), 5.77 (1H, dt, ^3J 12.0 and 6.4) and 4.34 (2H, dd, ^3J 6.4, ^4J 1.0); δ_C 137.00 (quat), 134.71 (quat), 128.37 (quat), 126.10, 124.93, 122.51, 120.58, 119.77, 111.09, 104.78 and 59.29 (CH_2); *m/z* 173 (M^+, 93%), 155 (29), 154 (70), 144 (82), 143 (31), 130 (100), 117 (61) and 115 (27).

9*H*-Pyrrolo[1,2-*a*]indole 369.

Pyrolysis [T_i 60 °C, T_f 750 °C, P_{range} 0.020-0.026 Torr, *t* 10 min] of *cis-3-(1H-indol-2-yl)-prop-2-en-1-ol* **367** (25 mg, 0.14 mmol) gave 9*H*-pyrrolo[1,2-*a*]indole **369** as a pale yellow solid (20 mg, 91%);[122] δ_H 7.31 (1H, m), 7.22 (1H, m), 7.19 (1H, m), 7.04-6.97 (2H, m), 6.31 (1H, t, ^3J 3.1), 6.03 (1H, m) and 3.76 (2H, s) (in agreement with literature data[122]); δ_C 141.02 (quat), 135.34 (quat), 134.80 (quat), 127.25, 125.70, 122.91, 112.93, 109.57 (2CH), 101.49 and 28.90 (CH_2).

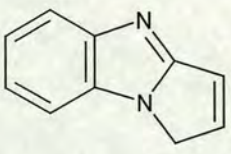


***cis*-3-(1*H*-Benzimidazol-2-yl)-prop-2-en-1-ol 68.**



Using oven dried glassware, a solution of pyrrolo[1,2-*a*]benzimidazol-1-one **280** (310 mg, 1.8 mmol) in dry THF (2 cm^3) was added to a suspension of lithium aluminium hydride (69 mg, 7.2 mmol) in dry THF (5 cm^3) under a nitrogen atmosphere at such a rate as to produce gentle reflux. Decolourisation occurred over 15 min. Wet ether (20 cm^3), water (20 cm^3) and a solution of potassium tartrate (20%, 10 cm^3) were added and the solution shaken vigorously then filtered through a pad of celite. The solution was adjusted to pH 7 then continually extracted into DCM for 48 h after which organic extracts were concentrated and absorbed onto silica. Dry flash chromatography separated side-products and the ring-opened product was washed off the column with methanol. The crude product was concentrated to ~1 cm^3, filtered through a celite pad to removed traces of silica and left to evaporate to dryness at atmospheric pressure whereupon crystallisation occurred. The product was washed with acetone (5 drops) at the water pump to give *cis-3-(1H-benzimidazol-2-yl)-prop-2-en-1-ol* **368** (20 mg, 6%) mp 157-159 °C; (Found: M^+ 174.0792. $C_{11}H_{10}N_2O$ requires *M* 174.0793); δ_H ([$^2H_6$] DMSO) 7.48-7.32 (2H, m), 7.07 (1H, dd, ^3J 6.1 and 3.1), 6.99 (1H, dd, ^3J 6.1 and 3.1), 6.28 (1H, d, ^3J 11.9 and 2.0), 6.09 (1H, dt, ^3J 11.9 and 5.3) and 4.54 (2H, dd, ^3J 5.3, ^4J 2.0); *m/z* 174 (M^+, 17%), 146 (29), 145 (52), 132 (50), 131 (21), 119 (31), 118 (47), 86 (88) and 84 (100).

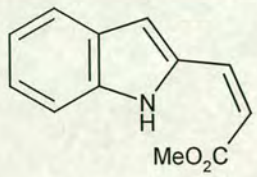
Attempted synthesis of 4*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazole 371.



Pyrolysis [T_i 60-220 °C, T_f 750 °C, P_{range} 0.020-0.026 Torr, *t* 10 min] of *cis-3-(1H-benzimidazol-2-yl)-prop-2-en-1-ol* **368** (20 mg, 0.11 mmol) to give 4*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazole **371** proved to be unsuccessful due to low substrate volatility at the inlet.

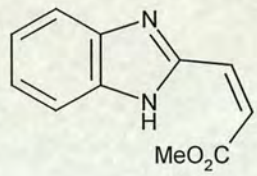
3.8.2 Ring opening reactions with methoxide

cis-3-(1*H*-Indol-2-yl)-acrylic acid methyl ester 372.



A solution of 3*H*-pyrrolo[1,2-*a*]indol-3-one **2** (30 mg, 0.18 mmol) and diisopropylethylamine (23 mg, 0.031 cm^3, 0.18 mmol) in methanol (10 cm^3) was stirred at room temperature for 2.5 h during which time the colour of the solution faded to pale yellow. Removal of the solvent gave *cis*-3-(1*H*-indol-2-yl)-acrylic acid methyl ester **372** (33 mg, 93%)[123] mp 101-102 °C [lit.,[123] 102 °C]; δ_H 11.75 (1H br s, NH), 7.55 (1H, d, ^3J 8.1), 7.37 (1H, dd, ^3J 8.1, ^4J 0.7), 7.20 (1H, t, ^3J 7.0, ^4J 0.7), 7.02 (1H, t, ^3J 7.0, ^4J 0.7), 6.87 (1H, d, ^3J 12.6), 6.70 (1H, s), 5.72 (1H, d, ^3J 12.6) and 3.76 (3H, s).

cis-3-(Benzimidazol-2-yl)-acrylic acid methyl ester 374.



A solution of pyrrolo[1,2-*a*]benzimidazol-1-one **280** (20 mg, 0.12 mmol) and diisopropylethylamine (2 drops, cat) were added together in methanol (5 cm^3) was stirred at room temperature for 5 min. during which time the solution decolourised. Removal of the solvent gave *cis-3-(benzimidazol-2-yl)-acrylic acid methyl ester* **374** (23 mg, 98%) mp 86-88 °C; (Found: M^+ 202.0742. $C_{11}H_{10}N_2O_2$ requires *M* 202.0742); δ_H ([$^2H_6$] DMSO) 7.92 (1H, d, ^3J 7.9), 7.87 (1H, d, ^3J 7.9), 7.45 (2H, m), 7.33 (1H, d, ^3J 12.8), 6.53 (1H, d, ^3J 12.8) and 4.00 (3H, s); δ_C 166.81 (quat), 146.82 (quat), 143.07 (quat), 133.84 (quat), 132.18, 123.90, 122.15, 121.23, 119.27, 112.52 and 52.01 (CH_3); *m/z* 202 (M^+, 100%), 171 (43), 170 (91), 144 (33), 143 (70), 142 (61), 118 (17) and 115 (16).

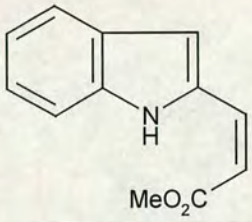
3.8.3 Reaction with aniline

3*H*-Pyrrolo[1,2-*a*]indol-3-one with aniline.

A solution of pyrrolo[1,2-*a*]indol-3-one **2** (28 mg, 0.17 mmol) in acetone (2 cm^3) was added to a solution of aniline (18 mg, 0.19 mmol) in water (20 cm^3) and heated under reflux for 9 h after which the reaction was evaporated to dryness and dried at the pump. A proton NMR spectrum showed recovered starting material only.

3.8.4 Reactions with *tert*-butylamine

3*H*-Pyrrolo[1,2-*a*]indol-3-one with *tert*-butylamine.



A solution of pyrrolo[1,2-*a*]indol-3-one **2** (20 mg, 0.12 mmol) in methanol (5 cm^3) was stirred with *tert*-butylamine (9 mg, 0.12 mmol) at room temperature for 72 h. No addition product was observed. Proton NMR spectroscopy indicated that ring-opened *cis*-3-(1*H*-indol-2-yl)-acrylic acid methyl ester **372** was the only product[123]; δ_H 11.75 (1H br s, NH), 7.53 (1H, d, ^3J 8.0), 7.37 (1H, dd, ^3J 8.0, ^4J 0.7), 7.24 (1H, t, ^3J 6.9, ^4J 0.7), 7.03 (1H, t, ^3J 6.9, ^4J 0.7), 6.85 (1H, d, ^3J 12.6), 6.70 (1H, s), 5.71 (1H, d, ^3J 12.6) and 3.76 (3H, s) (data compatible with spectrum reported above).

NMR tube reactions

To a sample of the benzopyrrolizinone in solvent (0.7 cm^3) was added *tert*-butylamine (1 equiv.) and the course of the reaction followed by proton NMR spectroscopy (see discussion section). The benzopyrrolizinone, solvent and reaction time are indicated in each case.

(i) Pyrrolo[1,2-*a*]indol-3-one **2** (20 mg, 0.12 mmol), [$^2H_6$] acetone, 72 h. No reaction observed; only recovered starting material.

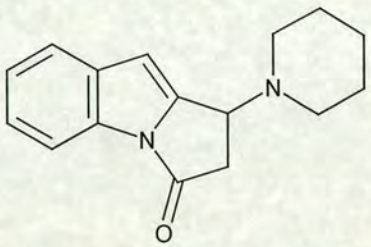
(ii) 9-Methyl-3*H*-pyrrolo[1,2-*a*]indol-3-one **78** (10 mg, 0.05 mmol), [$^2H_6$] acetone, 96 h. No reaction observed; only recovered starting material.

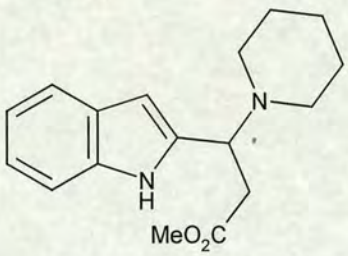
3.8.5 Reactions with piperidine

NMR tube reactions

To a sample of the benzopyrrolizinone in solvent (0.7 cm^3) was added piperidine (1 equiv.) and the course of the reaction followed by proton NMR spectroscopy (see discussion section). The benzopyrrolizinone, solvent and reaction time are indicated in each case. No yields were determined.

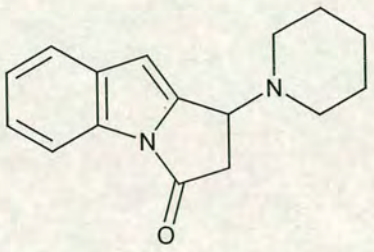
(i) Pyrrolo[1,2-*a*]indol-3-one **2** (20 mg, 0.12 mmol), [$^2H_4$] MeOH, 12 h. Two major products formed in 50:50 ratio (by examination of the integrals of characteristic proton NMR signals in the spectrum of the crude reaction mixture) co-eluting from dry flash column: *1,2-dihydro-1-piperidin-1-yl-3H-pyrrolo[1,2-a]indol-3-one* **375**; δ_H (aromatics indistinguishable), 6.39 (1H, s), 4.37 (1H, ddd, ^3J 8.2 and 3.4, ^4J 1.0), 3.15 (1H, dd, ^3J 18.6 and 8.3), 2.95 (1H, dd, ^3J 18.6 and 3.4), 2.52 (2H, quin, ^3J 10.7 and 5.4), 2.30 (2H, quin, ^3J 10.7 and 5.4) and 1.57-1.48 (6H, m); δ_C 170.08 (quat), 142.03 (quat), 134.47 (quat), 124.01, 123.73, 120.83, 113.75, 102.96, 57.87, 49.69 ($2CH_2$), 38.49 (CH_2), 25.74 ($2CH_2$) and 24.10 (CH_2) (one quaternary overlapping); *m/z* (FAB) 255 (MH^+, 13%): *3-(1H-indol-2-yl)-3-piperidin-1-yl-propionic acid methyl ester* **376**; δ_H 7.04 (1H, td, ^3J 7.9, ^4J 1.3), 6.98 (1H, td, ^3J 7.9, ^4J 1.3), (other aromatics indistinguishable), 6.24 (1H, t, ^4J 0.9), 4.29 (1H, q, ^3J 8.3 and 5.2), 3.61 (3H, s), 2.90 (1H, dd, ^3J 15.3 and 5.2), 2.75 (1H, dd, ^3J 15.3 and 8.3), 2.45-2.41 (4H, m), 1.57-1.48 (2H, m) and 1.42-1.34 (4H, m); δ_C 172.52 (quat), 135.72 (quat), 130.02 (quat), 128.05 (quat), 121.54, 120.11, 119.37, 110.70, 100.38, 60.02, 51.79 (CH_3), 50.22 ($2CH_2$), 33.40



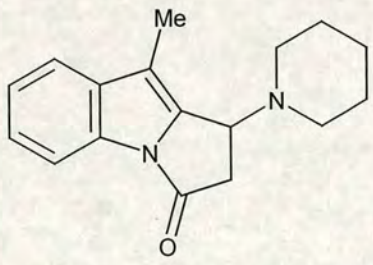


(CH_2), 26.00 ($2CH_2$) and 24.10 (CH_2) (good comparison with literature data); *m/z* (FAB) 287 (MH^+, 9%).

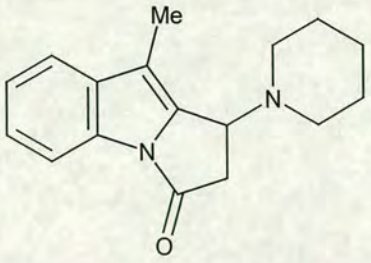
(ii) Pyrrolo[1,2-*a*]indol-3-one **2** (20 mg, 0.12 mmol), [$^2H_6$] acetone, 1.5 h. Solution decolourised to give *1,2-dihydro-1-piperidin-1-yl-3H-pyrrolo[1,2-a]indol-3-one* **375**, mp 146-148 °C; (Found M^+, 254.1423. $C_{16}H_{18}N_2O$ requires M, 254.1419); δ_H ([$^2H_6$] acetone) 8.00 (1H, m), 7.48 (1H, m), 7.25-7.18 (2H, m), 6.40 (1H, t, ^4J 1.1), 4.39 (1H, ddd, ^3J 8.3 and 3.3, ^4J 1.1), 3.17 (1H, dd, ^3J 18.6 and 8.3), 2.96 (1H, dd, ^3J 18.6 and 3.3), 2.53 (2H, quin, ^3J 10.6 and 5.3), 2.31 (2H, quin, ^3J 10.6 and 5.3) and 1.58-1.49 (6H, m); δ_C ([$^2H_6$] acetone) 170.11 (quat), 142.05 (quat), 134.49 (quat), 124.05, 123.77, 120.85, 113.80, 103.01, 57.91, 49.73 ($2CH_2$), 38.52 (CH_2), 25.77 ($2CH_2$) and 24.11 (CH_2) (one quaternary overlapping); *m/z* 254 (M^+, 66%), 212 (34), 171 (84), 170 (89), 143 (71), 142 (56), 141 (82), 117 (100), 90 (74), 89 (65) and 84 (90).



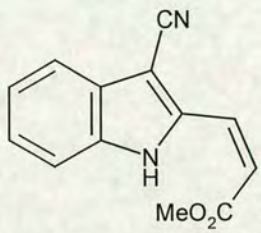
(iii) 9-Methyl-3*H*-pyrrolo[1,2-*a*]indol-3-one **78** (10 mg, 0.05 mmol), [$^2H_4$] MeOH, 72 h. NMR analysis showed characteristic 1 : 2 proton signals at 4.45 and 2.97 ppm and a mass spectrum gave *m/z* (FAB) 269 (M^+, 47%) indicating formation of the addition product **377** (see discussion section 2.4.3.3). No methoxide ring-opened product was present.

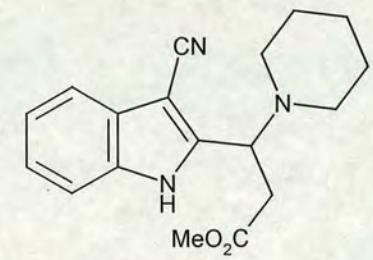


(iv) 9-Methyl-3*H*-pyrrolo[1,2-*a*]indol-3-one **78** (10 mg, 0.05 mmol), [$^2H_6$] acetone, 72 h. NMR analysis showed characteristic 1 : 2 proton signals at 4.45 and 2.97 ppm and a mass spectrum gave *m/z* (FAB) 269 (M^+, 78%) indicating formation of the addition product **377** (see discussion section 2.4.3.3).



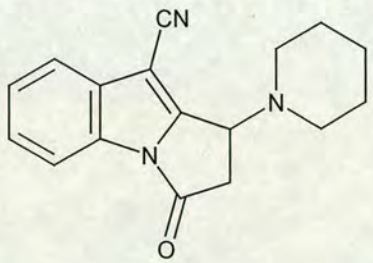
(v) 9-Cyano-3*H*-pyrrolo[1,2-*a*]indol-3-one **338** (10 mg, 0.05 mmol), [$^2H_4$] MeOH, 12h. A proton NMR indicated the reaction product to be a 2 : 1 mixture of methoxide ring-opened product and methoxide ring-opened addition product: *cis-3-(3-cyano-1H-indol-2-yl)-acrylic acid methyl ester* **379**; δ_H 7.67 (1H, dd, ^3J 8.1, ^4J 1.0), 7.44 (1H, dt, ^3J 8.2, ^4J 1.0), 7.32 (1H, td, ^3J 8.2, ^4J 1.2), 7.12 (1H, d, ^3J 12.7), 6.04 (1H, d, ^3J 12.7) and 3.82 (3H, s); *m/z* (FAB) 227 (MH^+, 65%) [identified by comparison with an authentic sample prepared as follows: a solution of 9-cyano-3*H*-pyrrolo[1,2-*a*]indol-3-one **338** (8 mg, 0.04 mmol) in methanol (3 cm^3) containing diisopropylethylamine (3 drops) was stirred at room temperature and decolourised over 2 min after which removal of solvent by rotary evaporator gave *cis-3-(3-cyano-1H-indol-2-yl)-acrylic acid methyl ester* **379** (9 mg, 96%); (Found M^+, 226.0747. $C_{13}H_{10}N_2O_2$ requires M, 226.0742); δ_H 12.43 (NH, br s), 7.67 (1H, dd, ^3J 8.1, ^4J 1.1), 7.44 (1H, dt, ^3J 8.1, ^4J 1.1), 7.32 (1H, td, ^3J 8.1, ^4J 1.1), 7.21 (1H, td, ^3J 8.1, ^4J 1.1), 7.12 (1H, d, ^3J 12.7), 6.04 (1H, d, ^3J 12.7) and 3.82 (3H, s);





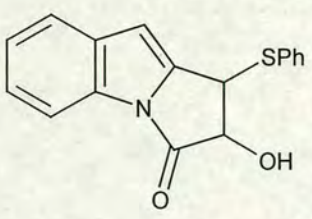
δ_C 168.41 (quat), 138.56 (quat), 135.77 (quat), 130.58, 127.39 (quat), 126.29, 122.64, 119.98, 119.65 (quat), 117.94, 115.10 (quat), 112.72 and 52.50; *m/z* 226 (M^+, 91%), 195 (55), 194 (87), 168 (61), 167 (67), 166 (100), 140 (49), 139 (56), 115 (39) and 114 (44)]: *3-(3-cyano-1H-indol-2-yl)-3-piperidin-1-yl-propionic acid methyl ester* **378**; δ_H (aromatic signals indistinguishable) 4.27 (1H, dd, ^3J 7.0 and 5.9), 3.64 (3H, s), 2.94 (2H, dd, ^3J 7.0, 5.9, 3.0 and 1.9), 2.48-2.30 (4H, m) and 1.55-1.45 (6H, m); *m/z* (FAB) 312 (MH^+, 50%).

(vi) 9-Cyano-3*H*-pyrrolo[1,2-*a*]indol-3-one **338** (10 mg, 0.05 mmol), [$^2H_6$] acetone, 1h. A proton NMR and mass spectrum indicated presence of addition product *1,2-dihydro-1-piperidin1-1-yl-9-cyano-3H-pyrrolo[1,2-a]indol-3-one* **380**, identified characteristic proton NMR signals; δ_H 4.40 (1H, dd, ^3J 9.6 and 3.9), 3.26 (1H, dd, ^3J 15.6 and 9.6) and 2.90 (1H, dd, ^3J 15.6 and 3.9); *m/z* (FAB) 280 (MH^+, 31%).



3.8.6 Reactions with thiophenol

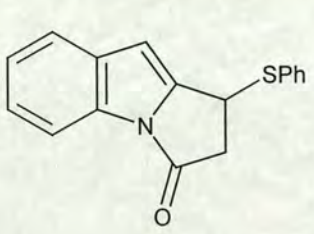
1,2-Dihydro-1-phenylthio-2-hydroxy-3*H*-pyrrolo[1,2-*a*]indol-3-one 382.



Pyrrolo[1,2-*a*]indol-3-one **2** (20 mg, 0.12 mmol) and thiophenol (13 mg, 0.12 mmol) were stirred together for 30 min in methanol (4 cm^3) at room temperature during which time the colour faded. A ^{13}C NMR spectrum indicated that there was no CH_2 moiety present. T. L. C. analysis on silica showed one major product. Separation by dry flash chromatography using 20% ethyl acetate in hexane afforded a product that was identified by NMR spectroscopy and mass spectroscopy (see discussion section 2.4.3.4) as *1,2-dihydro-1-phenylthio-2-hydroxy-3H-pyrrolo[1,2-a]indol-3-one* **382** (35 mg, 32% after purification) mp 107-109 °C; (Found M^+, 295.0667. $C_{17}H_{13}NO_2S$

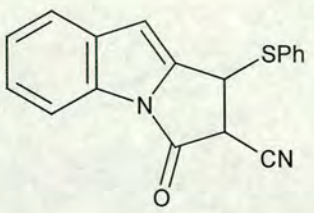
requires M, 295.0661); δ_H 8.02 (1H, m), 7.59-7.47 (3H, m), 7.36-7.22 (5H, m), 6.48 (1H, s), 5.29 (1H, d, ^3J 3.4) and 4.25 (1H, d, ^3J 3.4); δ_C 166.82 (quat), 141.40 (quat), 134.38 (quat), 132.95 (2CH), 131.33 (quat), 130.37 (quat), 129.13 (2CH), 128.45, 124.63, 124.52, 121.38, 114.08, 102.76, 70.13 and 60.41; *m/z* 295 (M^+, 38%), 277 (27), 218 (37), 170 (63), 169 (58), 150 (43), 145 (100), 144 (73), 130 (25), 109 (60) and 89 (52).

1,2-Dihydro-1-phenylthio-3*H*-pyrrolo[1,2-*a*]indol-3-one 381.



Pyrrolo[1,2-*a*]indol-3-one **2** (20 mg, 0.12 mmol) and thiophenol (13 mg, 0.12 mmol) were added together in [$^2H_6$] acetone. The solution decolourised over 5 min and a proton NMR indicated a single addition product, *1,2-dihydro-1-phenylthio-3H-pyrrolo[1,2-a]indol-3-one* **381** that was purified by dry flash chromatography using 5% ethyl acetate in hexane (30 mg, 92%) mp 104-106 °C; (Found M^+, 279.0719. $C_{17}H_{13}NOS$ requires M, 279.0718); δ_H 7.94 (1H, m), 7.43 (1H, m), 7.38-7.34 (2H, m), 7.26-7.17 (5H, m), 6.17 (1H, dd, ^4J 1.1 and 0.9), 4.77 (1H, ddd, ^3J 8.2 and 3.1, ^4J 1.3), 3.44 (1H, dd, ^3J 18.7 and 8.3) and 3.00 (1H, dd, ^3J 18.7 and 3.1); δ_C 168.80 (quat), 143.11 (quat), 134.59 (quat), 132.88 (2CH), 132.57 (quat), 130.21 (quat), 129.15 (2CH), 128.36, 124.20, 124.02, 121.05, 113.68, 102.08, 43.19 (CH_2) and 38.05; *m/z* 279 (M^+, 32%), 218 (56), 171 (54), 170 (100), 169 (44), 142 (47), 117 (34), 115 (42) and 109 (49).

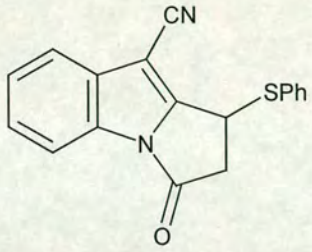
1,2-Dihydro-1-phenylthio-2-cyano-3*H*-pyrrolo[1,2-*a*]indol-3-one 383.



2-Cyanopyrrolo[1,2-*a*]indol-3-one **326** (65 mg, 0.06 mmol) and thiophenol (37 mg, 0.06 mmol) were added together in methanol (6 cm^3) and stirred at room temperature during which time the colour faded slightly. The reaction was concentrated and dried to give crude *1,2-Dihydro-1-phenylthio-9-cyano-3H-pyrrolo[1,2-a]indol-3-one* **383** (58 mg, 95%); (Found MH^+, 304.0740. $C_{18}H_{12}N_2OS$ requires MH, 304.0749); δ_H 7.96 (1H, m), 7.59-7.08 (8H, m), 6.55 (1H, s), 5.05 (1H, d, ^3J 4.2) and 4.14 (1H, d, ^3J 4.2); δ_C 159.83 (quat), 142.91 (quat), 133.77 (2CH),

129.69 (2CH), 128.90, 125.33, 124.14, 121.56, 113.93, 104.34, 45.41 and 44.16 (other quaternaries indistinguishable); *m/z* (e.i.) 304 (M^+, 0.2%), 276 (0.2), 246 (0.3), 226 (1.4), 218 (1.4), 194 (100), 165 (15), 139 (32) and 110 (48); *m/z* (FAB) 305 (MH^+, 90).

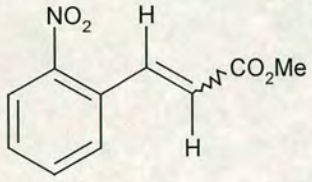
1,2-Dihydro-1-phenylthio-9-cyano-3*H*-pyrrolo[1,2-*a*]indol-3-one 384.



9-Cyanopyrrolo[1,2-*a*]indol-3-one **338** (12 mg, 0.06 mmol) and thiophenol (7 mg, 0.06 mmol) were added together in methanol (2 cm^3) and left to stand at room temperature over 20 h. Removal of solvent under reduced pressure at the pump afforded *1,2-dihydro-1-phenylthio-9-cyano-3H-pyrrolo[1,2-a]indol-3-one* **384** (identified by comparison of the proton NMR spectrum with that of parent compound **381**) (crude 18 mg, 95%); δ_H 7.91 (1H, m), 7.62 (1H, m), 7.43-7.16 (7H, m), 4.85 (1H, dd, ^3J 8.2 and 2.7), 3.55 (1H, dd, ^3J 19.1 and 8.2) and 3.12 (1H, dd, ^3J 19.1 and 2.7).

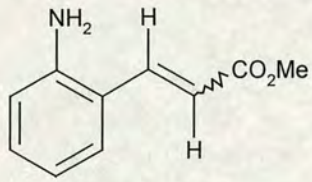
3.9 Flash vacuum pyrolysis of methyl 2-(pyrrol-1-yl)cinnamic acid methyl ester and novel synthesis of phenanthrene

Methyl-2-nitrocinnamate 390.



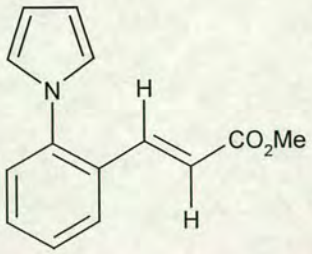
A solution of 2-nitrocinnamic acid **389** (4.84 g, 25 mmol) and anhydrous potassium carbonate (3.82 g) in dimethylformamide (30 cm^3) was stirred magnetically. Iodomethane (3.92 g, 28 mmol) was added dropwise over 10 min, and the solution left to stir for 24 h. The yellow solution was diluted with water (50 cm^3) and extracted with diethyl ether (3 × 50 cm^3). The ether was washed with water (6 × 50 cm^3) and dried over $MgSO_4$. The ether was removed under reduced pressure to give the solid product **390** (3.31 g, 64%), mp 71-73 °C (lit.,[124] 72-73 °C) δ_H 8.03 (1H, d, ^3J 15.9), 7.98 (1H, d, ^3J 10.0), 7.62-7.43 (3H, m), 6.30 (1H, d, ^3J 15.9) and 3.76 (3H, s).

Methyl-2-aminocinnamate 391.



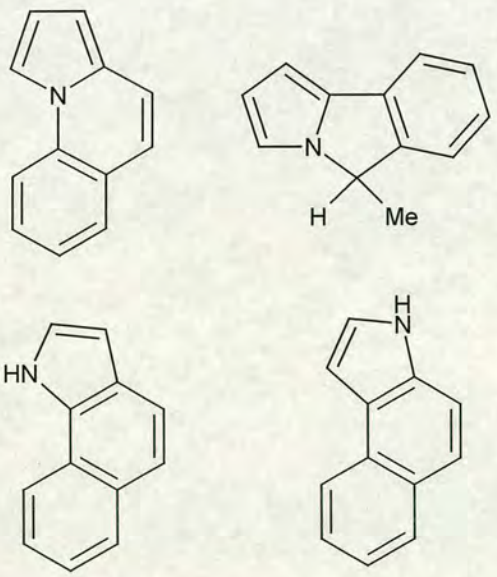
Methyl-2-nitrocinnamate **390** (3.31 g, 16 mmol) was dissolved in methanol (60 cm^3). Water (7 cm^3) and ammonium chloride (1.35 g, 25 mmol) were added. The solution was stirred and zinc dust (9.00 g) added over 15 min. After the initial reaction had subsided the solution was heated under reflux for 2 h and filtered hot through celite. The solution was diluted with water (100 cm^3) and cooled in ice to precipitate solid zinc salt by-products. The solid was filtered off and the solution extracted with dichloromethane (3 × 75 cm^3). The dichloromethane layer was separated from the aqueous layer and concentrated to give methyl-2-aminocinnamate **391** as a yellow solid [125] (1.43 g, 51%) δ_H 7.77 (1H, d, ^3J 15.7), 7.31 (1H, dd, ^3J 8.1, ^4J 2.8), 7.08 (1H, d, ^3J 8.1), 6.73-6.61 (2H, m), 6.26 (1H, d, ^3J 15.7), 3.91 [2H, br s, (NH_2)] and 3.72 (3H, s).

Methyl 2-(pyrrol-1-yl)cinnamate 388.



Methyl-2-aminocinnamate **391** (0.92 g, 5 mmol) was added to 2,5-dimethoxytetrahydrofuran (0.68 g, 5 mmol) and glacial acetic acid (1 cm^3) and heated under reflux for 20 min. The acetic acid was removed under reduced pressure and the crude product distilled using a Kugelrohr. The product was then purified by dry flash chromatography on silica (15% ethyl acetate in hexane) to give *methyl 2-(pyrrol-1-yl)cinnamate* **388** (0.64 g, 54%), mp 39-41 °C, bp 92 °C (0.2 Torr) [(FAB) Found MH^+ 228.1024. $C_{14}H_{14}NO_2$ requires *MH* 228.1025]; δ_H 7.69-7.25 (4H, m), 7.56 (2H, d, ^3J 16.0), 6.81 (2H, s), 6.35 (1H, s), 6.32 (1H, d, ^3J 16.0) and 3.76 (3H, s); δ_C 166.82 (quat), 140.53 (quat), 140.34, 130.49, 130.03 (quat), 127.54, 127.36, 126.55, 122.64 (2C), 119.90, 109.78 (2C) and 51.62 (CH_3); *m/z* (e.i.) 227 (M^+, 0.6%), 169 (42), 168 (100), 167 (85), 166 (55), 140 (23), 139 (29), 128 (20), 115 (22), 83 (25), 75 (25), 63 (24) and 51 (29); *m/z* (FAB) 228 (MH^+, 63%).

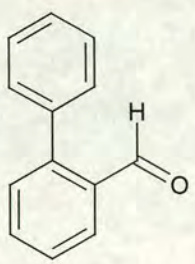
FVP of methyl 2-(pyrrol-1-yl)cinnamate 388.



Small scale pyrolyses (50 mg, 0.22 mmol, T_i 50-100 °C, P_{range} 0.01-0.05 Torr, *t* 15 min) of methyl 2-(pyrrol-1-yl)cinnamate **388** were performed at furnace temperatures of 800, 850 and 900 °C. The optimum temperature for complete conversion of starting material was 850 °C. A preparative pyrolysis (0.363 g, 1.6 mmol, T_f 850 °C, T_i 50-100 °C, P_{range} 0.01-0.07 Torr, *t* 100 min) afforded four major products that were separated by dry flash chromatography using a hexane/ethyl acetate gradient as eluent (isolated products 0.146 g, 40%). The reaction products identified were, in order of elution: pyrrolo[1,2-*a*]quinoline **392** (21 mg, 8%) δ_H 7.88 (1H, d, ^3J 8.8), 7.85 (1H, dd, ^3J 2.9, ^4J 1.4), 7.64 (1H, dd, ^3J 7.8, ^4J

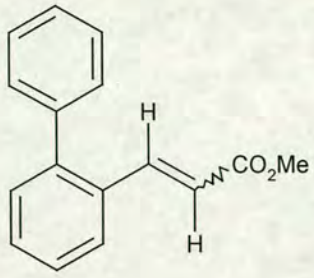
1.5), 7.49 (1H, ddd, ^3J 8.6 and 7.2, ^4J 1.5), 7.34-7.26 (2H, m), 6.98 (1H, d, ^3J 8.8), 6.78 (1H, dd, ^3J 3.8 and 2.9) and 6.52 (1H, dd, ^3J 3.8, ^4J 1.4); δ_C 133.3 (quat), 130.9 (quat), 128.4, 127.5, 123.7 (quat), 123.3, 118.8, 118.5, 114.0, 112.6, 111.8 and 102.6; *m/z* 167 (M^+, 100%), 166 (20), 139 (13), 123 (17), 105 (28), 69 (32), 57 (34), 43 (48) and 39 (19), spectra consistent with those in literature:[99] 5-methyl-5*H*-pyrrolo[1,2-*a*]isoindole **394** (30 mg, <11%) as major component of impure fraction (Found M^+ 169.0893. $C_{12}H_{11}N$ requires *M* 169.0892); δ_H (360 MHz) 7.52 (1H, d, ^3J 7.4), 7.34 (2H, m), 7.21 (1H, t, ^3J *ca.* 7.4), 6.97 (1H, m), 6.41 (1H, dd, ^3J 3.5 and 2.6), 6.33 (1H, dd, ^3J 3.5, ^4J 1.1), 5.08 (1H, q, ^3J 6.9) and 1.68 (3H, d, ^3J 6.9); δ_C (quaternary signals not quoted) 127.85, 124.73, 122.16, 118.38, 114.65, 112.51, 97.90, 56.90 and 20.89 (CH_3); *m/z* 169 (M^+, 88%) and 154 (100): 1*H*-benz[*g*]indole **396** as the minor component in a mixture with **397** (37 mg, 14% total) δ_H 8.85 (1H, br, NH), 7.96-7.91 (2H, m), 7.74 (1H, dd, ^3J 8.8, ^4J 0.7), 7.63-7.40 (3H, m), 7.24 (1H, m) and 6.70 (1H, dd, ^3J 3.0, ^4J 2.1); δ_C (CH signals only) 128.7, 125.3, 123.7, 122.6, 120.7, 120.6, 119.2 and 104.2 (spectra compatible with literature data[101]): a pure fraction of 3*H*-benz[*e*]indole **397** was also obtained, δ_H (360 MHz) 8.42 (1H, br, NH), 8.27 (1H, dm, ^3J 8.1, ^4J 1.4, ^5J and ^nJ 0.7), 7.94 (1H, dm, ^3J 8.1, ^4J 1.4, ^5J and ^nJ 0.7), 7.64 (1H, d, ^3J 8.9), 7.59 (2H, ddd, ^3J 8.1 and 6.9, ^4J 1.4), 7.32 (1H, ddd, ^3J 2.9, ^4J 2.5 and ^nJ 0.3) and 7.14 (1H, ddd, ^3J 2.9, ^4J 2.1 and ^nJ 0.9) and 6.72 (1H, m); δ_C (90 MHz) 132.60 (quat), 129.58 (quat), 128.93, 128.62 (quat), 126.19, 123.75, 123.41 (2C), 123.23 (quat), 122.59, 113.16 and 102.37; *m/z* 167 (M^+, 100%), 155 (12), 140 (23), 139 (32), 105 (14), 86 (35), 84 (68), and 77 (14) (spectra compatible with literature data[102]).

Biphenyl 2-carbaldehyde 406.



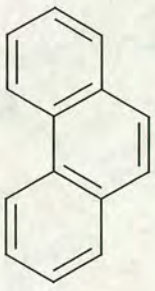
Biphenyl 2-methanol (0.25 g, 1.36 mmol) was added to a suspension of manganese dioxide (1.25 g) in toluene (25 cm^3) and heated under reflux for 3 h. The solution was then filtered through celite, dried over magnesium sulfate and the solvent removed under reduced pressure to give biphenyl 2-carbaldehyde **406** as a yellow oil[126] (0.24 g, 97%) bp 137-139 °C (5 Torr) [lit.,[126] 138-140 (5 Torr)] δ_H 9.99 (1H, s), 8.04 (1H, dd, ^3J 7.7, ^4J 0.9), 7.63 (1H, dd, ^3J 7.7, ^4J 1.4) and 7.53-7.36 (7H, m).

3-(Biphenyl-2-yl)-acrylic acid methyl ester 405.



To a stirred solution of biphenyl 2-aldehyde **406** (0.24 g, 1.31 mmol) in toluene (25 cm^3) was added methyl (triphenylphosphoranylidene)acetate (0.50 g, 1.5 mmol) and the reaction allowed to stir overnight. The solution was absorbed onto silica and purified by dry flash chromatography (10% ethyl acetate in hexane as eluent) followed by distillation in Kugelrohr equipment to give a 3 : 1 *E*/*Z* isomer mixture of 3-(biphenyl-2-yl)-acrylic acid methyl ester **405** as a pale yellow oil[103] (0.25g, 77%) bp 103-105 °C (0.3 Torr) [lit.[103] 184 °C (4 mmHg)] δ_{Htrans} 7.83 (1H, d, ^3J 15.9), 7.49-7.26 (9H, m), 6.41 (1H, d, ^3J 15.9) and 3.65 (3H,s); δ_{Hcis} 6.86 (1H, d, ^3J 12.3), 5.93 (1H, d, ^3J 12.3) and 3.60 (3H, s) (other signals indistinguishable); δ_{Ctrans} 167.12 (quat), 143.79, 142.77 (quat), 139.71 (quat), 132.38 (quat), 130.39, 129.71, 129.63 (2CH), 128.15, 127.91, 127.48, 127.41, 126.66, 118.60 and 51.44 (CH_3); δ_{Ccis} 166.62 (quat), 144.18, 141.10 (quat), 140.33 (quat), 133.48 (quat), 129.77, 129.25, 128.72, 128.26, 127.67, 127.22, 126.52, 123.90, 123.53, 119.58 and 51.13 (CH_3); *m/z* 238 (M^+, 65%), 207 (30), 181 (31), 180 (62), 179 (100), 178 (98), 177 (64), 176 (55), 165 (56), 152 (52), 151 (36) and 89 (76).

FVP of 3-(biphenyl-2-yl)-acrylic acid methyl ester 405.



Small scale pyrolyses (30 mg, 0.13 mmol, T_i 165 °C, P_{range} 0.01-0.06 Torr, *t* 9 min) of 3-(biphenyl-2-yl)-acrylic acid methyl ester **405** were performed at furnace temperatures of 850, 900 and 950 °C. The optimum temperature for complete conversion of starting material was 950 °C. A preparative pyrolysis (100 mg, 0.42 mmol, T_f 950 °C, T_i 165 °C, P_{range} 0.02-0.07 Torr, *t* 18 min) gave phenanthrene **408** as a white solid (71 mg, 95%) mp 100-102 °C (lit.,[104] 99-101 °C), δ_H 8.73 (2H, d, ^3J 8.2), 7.93 (2H, dd, ^3J 8.2, ^4J 1.4), 7.80 (2H, s) and 7.76-7.62 (4H, m) (spectrum compatible with literature data[104]). Pyrolyses performed at 850 and 900 °C afforded phenanthrene as well as recovered starting material (26 and 9% respectively) and a second product identified as methyl 9,10-dihydrophenanthrene-9-carboxylate **407** (18 and 4% respectively) δ_H (aromatic

signals not quoted) 3.81 (1H, t, ^{3}J 5.9), 3.54 (3H, s), 3.24 (1H, dd, ^{3}J 15.4 and 5.9) and 3.03 (1H, dd, ^{3}J 15.4 and 5.9) (spectrum compatible with literature data[127]).

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APPENDIX

Table 3. Bond lengths [A] and angles [deg] for hmrt01.

C(1)-C(2)	1.333(2)
C(1)-C(9A)	1.448(2)
C(2)-C(3)	1.489(2)
O(3)-C(3)	1.2092(19)
C(3)-N(4)	1.3937(18)
N(4)-C(9A)	1.3894(18)
N(4)-C(4A)	1.3950(17)
C(4A)-C(5)	1.3806(19)
C(4A)-C(8A)	1.4095(18)
C(5)-C(6)	1.383(2)
C(6)-C(7)	1.384(2)
C(7)-C(8)	1.380(2)
C(8A)-C(8)	1.396(2)
C(8A)-C(9)	1.445(2)
C(9A)-C(9)	1.352(2)
C(1')-C(2')	1.331(2)
C(1')-C(9A')	1.452(2)
C(2')-C(3')	1.488(2)
O(3')-C(3')	1.2080(18)
C(3')-N(4')	1.3945(17)
N(4')-C(9A')	1.3906(17)
N(4')-C(4A')	1.3988(16)
C(4A')-C(5')	1.3765(19)
C(4A')-C(8A')	1.4102(19)
C(5')-C(6')	1.386(2)
C(6')-C(7')	1.390(2)
C(7')-C(8')	1.378(2)
C(8')-C(8A')	1.395(2)
C(8A')-C(9')	1.447(2)
C(9A')-C(9')	1.345(2)
C(2)-C(1)-C(9A)	108.61(14)
C(1)-C(2)-C(3)	109.79(14)
O(3)-C(3)-N(4)	125.74(15)
O(3)-C(3)-C(2)	130.55(15)
N(4)-C(3)-C(2)	103.71(13)
C(9A)-N(4)-C(3)	111.39(12)
C(9A)-N(4)-C(4A)	109.31(11)
C(3)-N(4)-C(4A)	139.28(12)
C(5)-C(4A)-N(4)	130.88(12)
C(5)-C(4A)-C(8A)	122.82(13)
N(4)-C(4A)-C(8A)	106.29(11)
C(4A)-C(5)-C(6)	116.99(14)
C(5)-C(6)-C(7)	121.43(15)
C(8)-C(7)-C(6)	121.51(15)
C(8)-C(8A)-C(4A)	118.59(13)
C(8)-C(8A)-C(9)	133.71(13)
C(4A)-C(8A)-C(9)	107.69(12)
C(7)-C(8)-C(8A)	118.66(14)
C(9)-C(9A)-N(4)	109.62(13)
C(9)-C(9A)-C(1)	143.89(14)
N(4)-C(9A)-C(1)	106.49(13)
C(9A)-C(9)-C(8A)	107.08(12)
C(2')-C(1')-C(9A')	108.35(13)
C(1')-C(2')-C(3')	110.19(13)
O(3')-C(3')-N(4')	126.13(13)
O(3')-C(3')-C(2')	130.27(14)
N(4')-C(3')-C(2')	103.59(12)
C(9A')-N(4')-C(3')	111.43(11)
C(9A')-N(4')-C(4A')	109.45(11)

C(3')-N(4')-C(4A')	139.09(12)
C(5')-C(4A')-N(4')	131.07(12)
C(5')-C(4A')-C(8A')	123.15(12)
N(4')-C(4A')-C(8A')	105.77(11)
C(4A')-C(5')-C(6')	116.76(14)
C(5')-C(6')-C(7')	121.51(15)
C(8')-C(7')-C(6')	121.23(14)
C(7')-C(8')-C(8A')	118.84(15)
C(8')-C(8A')-C(4A')	118.50(14)
C(8')-C(8A')-C(9')	133.49(14)
C(4A')-C(8A')-C(9')	108.00(12)
C(9')-C(9A')-N(4')	109.74(12)
C(9')-C(9A')-C(1')	143.82(14)
N(4')-C(9A')-C(1')	106.43(12)
C(9A')-C(9')-C(8A')	107.03(12)

Table A – bond lengths and bond angles of **2**

Table 3. Bond lengths [A] and angles [deg] for hmrt02.

C(1)-C(11A)	1.386(11)
C(1)-C(2)	1.395(13)
C(2)-C(3)	1.381(12)
C(3)-C(4)	1.395(12)
C(4)-C(4A)	1.384(12)
C(4A)-C(11A)	1.395(11)
C(4A)-N(5)	1.409(11)
N(5)-C(6)	1.342(11)
N(5)-C(10B)	1.379(9)
C(6)-O(6)	1.228(17)
C(6)-C(6A)	1.505(12)
C(6A)-C(7)	1.374(11)
C(6A)-C(10A)	1.393(11)
C(7)-C(8)	1.395(13)
C(8)-C(9)	1.379(12)
C(9)-C(10)	1.402(13)
C(10)-C(10A)	1.396(12)
C(10A)-C(10B)	1.484(12)
C(10B)-C(11)	1.338(11)
C(11)-C(11A)	1.463(11)
C(11A)-C(1)-C(2)	114.9(18)
C(3)-C(2)-C(1)	130(2)
C(2)-C(3)-C(4)	114(2)
C(4A)-C(4)-C(3)	118(2)
C(4)-C(4A)-C(11A)	126.5(16)
C(4)-C(4A)-N(5)	126.2(16)
C(11A)-C(4A)-N(5)	107.3(11)
C(6)-N(5)-C(10B)	116.0(10)
C(6)-N(5)-C(4A)	137.4(13)
C(10B)-N(5)-C(4A)	106.5(9)
O(6)-C(6)-N(5)	128.9(16)
O(6)-C(6)-C(6A)	127.8(14)
N(5)-C(6)-C(6A)	102.1(11)
C(7)-C(6A)-C(10A)	124.5(15)
C(7)-C(6A)-C(6)	124.3(14)
C(10A)-C(6A)-C(6)	111.1(11)
C(6A)-C(7)-C(8)	121.7(18)
C(9)-C(8)-C(7)	114(2)
C(8)-C(9)-C(10)	126(2)
C(10A)-C(10)-C(9)	119(2)
C(6A)-C(10A)-C(10)	115.0(16)
C(6A)-C(10A)-C(10B)	104.5(11)
C(10)-C(10A)-C(10B)	140.5(17)
C(11)-C(10B)-N(5)	112.8(12)
C(11)-C(10B)-C(10A)	139.9(16)
N(5)-C(10B)-C(10A)	106.2(9)
C(10B)-C(11)-C(11A)	104.6(12)
C(1)-C(11A)-C(4A)	117.0(14)
C(1)-C(11A)-C(11)	135.1(14)
C(4A)-C(11A)-C(11)	107.9(11)

Table B – bond lengths and bond angles of **3**

Table 3. Bond lengths [A] and angles [deg] for rtbph2.

O(1)-C(3)	1.2199(19)
C(1)-C(10)	1.529(2)
C(1)-C(2)	1.536(2)
C(2)-C(3)	1.520(2)
C(3)-N(4)	1.3596(19)
N(4)-C(11)	1.4057(18)
N(4)-C(10)	1.478(2)
C(5)-C(11)	1.382(2)
C(5)-C(6)	1.398(2)
C(6)-C(7)	1.387(2)
C(7)-C(8)	1.391(2)
C(8)-C(12)	1.387(2)
C(9)-C(12)	1.513(2)
C(9)-C(10)	1.545(2)
C(11)-C(12)	1.393(2)
C(10)-C(1)-C(2)	103.17(12)
C(3)-C(2)-C(1)	104.09(12)
O(1)-C(3)-N(4)	125.54(14)
O(1)-C(3)-C(2)	128.10(14)
N(4)-C(3)-C(2)	106.36(13)
C(3)-N(4)-C(11)	130.49(13)
C(3)-N(4)-C(10)	114.37(12)
C(11)-N(4)-C(10)	110.69(12)
C(11)-C(5)-C(6)	117.54(14)
C(7)-C(6)-C(5)	120.36(15)
C(6)-C(7)-C(8)	121.24(14)
C(12)-C(8)-C(7)	119.03(15)
C(12)-C(9)-C(10)	103.07(12)
N(4)-C(10)-C(1)	102.34(12)
N(4)-C(10)-C(9)	103.82(12)
C(1)-C(10)-C(9)	120.33(13)
C(12)-C(11)-C(5)	122.80(14)
C(12)-C(11)-N(4)	109.02(13)
C(5)-C(11)-N(4)	128.17(14)
C(11)-C(12)-C(8)	119.02(15)
C(11)-C(12)-C(9)	110.36(13)
C(8)-C(12)-C(9)	130.55(15)

Table C - bond lengths and bond angles of **347**

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for rtbph2.

	x	y	z	U(eq)
H(1A)	5111	14586	6636	41
H(1B)	2550	13456	6311	41
H(2A)	2425	12215	3695	38
H(2B)	4885	12443	4418	38
H(5)	1339	6456	5692	32
H(6)	-114	4877	7445	36
H(7)	151	6569	9991	39
H(8)	1886	9843	10876	38
H(9A)	4820	12892	10065	40
H(9B)	2504	12663	8855	40
H(10)	6046	12651	7950	36

Table D – hydrogen coordinates for **347**

Table 3. Bond lengths [A] and angles [deg] for rt25a1.

C(1)-C(2)	1.3994(16)
C(1)-C(13)	1.3918(14)
C(1)-H(11)	1.000
C(2)-C(3)	1.3899(17)
C(2)-H(21)	1.000
C(3)-C(4)	1.4029(15)
C(3)-H(31)	1.000
C(4)-C(14)	1.3854(14)
C(4)-H(41)	1.000
N(5)-C(6)	1.3855(12)
N(5)-C(11)	1.4820(12)
N(5)-C(14)	1.4144(12)
C(6)-C(15)	1.4844(13)
C(6)-O(6)	1.2237(12)
C(7)-C(8)	1.3937(15)
C(7)-C(15)	1.3889(13)
C(7)-H(71)	1.000
C(8)-C(9)	1.3961(15)
C(8)-H(81)	1.000
C(9)-C(10)	1.3969(14)
C(9)-H(91)	1.000
C(10)-C(16)	1.3913(13)
C(10)-H(101)	1.000
C(11)-C(12)	1.5535(13)
C(11)-C(16)	1.5065(13)
C(11)-H(111)	1.000
C(12)-C(13)	1.5193(14)
C(12)-H(121)	1.000
C(12)-H(122)	1.000
C(13)-C(14)	1.3993(14)
C(15)-C(16)	1.3960(12)

C(2)-C(1)-C(13)	119.0(1)
C(2)-C(1)-H(11)	120.49(6)
C(13)-C(1)-H(11)	120.54(6)
C(1)-C(2)-C(3)	121.0(1)
C(1)-C(2)-H(21)	119.53(6)
C(3)-C(2)-H(21)	119.49(6)
C(2)-C(3)-C(4)	120.9(1)
C(2)-C(3)-H(31)	119.56(6)
C(4)-C(3)-H(31)	119.58(6)
C(3)-C(4)-C(14)	117.1(1)
C(3)-C(4)-H(41)	121.43(6)
C(14)-C(4)-H(41)	121.44(6)
C(6)-N(5)-C(11)	113.21(7)
C(6)-N(5)-C(14)	124.56(8)
C(11)-N(5)-C(14)	109.67(7)
N(5)-C(6)-C(15)	105.52(8)
N(5)-C(6)-O(6)	125.42(9)
C(15)-C(6)-O(6)	129.00(9)
C(8)-C(7)-C(15)	117.52(9)
C(8)-C(7)-H(71)	121.21(6)
C(15)-C(7)-H(71)	121.27(6)
C(7)-C(8)-C(9)	120.69(9)

C(7)-C(8)-H(81)	119.66(6)
C(9)-C(8)-H(81)	119.66(6)
C(8)-C(9)-C(10)	121.38(9)
C(8)-C(9)-H(91)	119.31(6)
C(10)-C(9)-H(91)	119.31(6)
C(9)-C(10)-C(16)	118.08(9)
C(9)-C(10)-H(101)	120.97(6)
C(16)-C(10)-H(101)	120.96(6)
N(5)-C(11)-C(12)	104.06(7)
N(5)-C(11)-C(16)	101.98(7)
C(12)-C(11)-C(16)	120.96(8)
N(5)-C(11)-H(111)	122.13(5)
C(12)-C(11)-H(111)	103.51(5)
C(16)-C(11)-H(111)	105.60(5)
C(11)-C(12)-C(13)	102.28(7)
C(11)-C(12)-H(121)	111.24(5)
C(13)-C(12)-H(121)	111.24(5)
C(11)-C(12)-H(122)	111.23(5)
C(13)-C(12)-H(122)	111.24(5)
H(121)-C(12)-H(122)	109.467
C(1)-C(13)-C(12)	130.70(9)
C(1)-C(13)-C(14)	119.0(1)
C(12)-C(13)-C(14)	110.13(8)
C(4)-C(14)-N(5)	127.58(9)
C(4)-C(14)-C(13)	123.05(9)
N(5)-C(14)-C(13)	109.34(8)
C(6)-C(15)-C(7)	128.24(9)
C(6)-C(15)-C(16)	109.33(8)
C(7)-C(15)-C(16)	122.29(9)
C(10)-C(16)-C(11)	130.39(9)
C(10)-C(16)-C(15)	120.05(9)
C(11)-C(16)-C(15)	109.55(8)

Table E – bond lengths and bond angles for **348**

Table 3. Bond lengths [A] and angles [deg] for rt29a1.

C(1)-C(2)	1.379(3)
C(1)-C(22)	1.384(2)
C(2)-C(3)	1.389(3)
C(3)-C(4)	1.384(3)
C(4)-C(5)	1.400(2)
C(5)-C(22)	1.408(2)
C(5)-C(6)	1.449(2)
C(6)-C(7)	1.348(2)
C(7)-N(21)	1.401(2)
C(7)-C(8)	1.497(2)
C(8)-C(18)	1.557(2)
C(8)-C(9)	1.558(2)
C(9)-O(10)	1.452(2)
C(9)-C(11)	1.510(2)
O(10)-C(17)	1.446(2)
C(11)-C(12)	1.378(2)
C(11)-C(16)	1.390(2)
C(12)-C(13)	1.390(3)
C(13)-C(14)	1.379(3)
C(14)-C(15)	1.396(2)
C(15)-C(16)	1.377(2)
C(16)-C(17)	1.511(2)
C(17)-C(18)	1.554(2)
C(18)-C(19)	1.507(2)
C(19)-O(20)	1.210(2)
C(19)-N(21)	1.380(2)
N(21)-C(22)	1.395(2)
C(2)-C(1)-C(22)	117.00(18)
C(1)-C(2)-C(3)	121.16(18)
C(4)-C(3)-C(2)	121.77(18)
C(3)-C(4)-C(5)	118.48(18)
C(4)-C(5)-C(22)	118.27(17)
C(4)-C(5)-C(6)	133.84(18)
C(22)-C(5)-C(6)	107.89(14)
C(7)-C(6)-C(5)	107.27(15)
C(6)-C(7)-N(21)	109.23(15)
C(6)-C(7)-C(8)	142.12(16)
N(21)-C(7)-C(8)	108.62(14)
C(7)-C(8)-C(18)	103.54(13)
C(7)-C(8)-C(9)	117.20(13)
C(18)-C(8)-C(9)	100.84(13)
O(10)-C(9)-C(11)	101.55(13)
O(10)-C(9)-C(8)	100.23(12)
C(11)-C(9)-C(8)	108.19(13)
C(17)-O(10)-C(9)	96.72(11)
C(12)-C(11)-C(16)	121.24(16)
C(12)-C(11)-C(9)	133.48(16)
C(16)-C(11)-C(9)	105.09(14)
C(11)-C(12)-C(13)	117.56(17)
C(14)-C(13)-C(12)	121.30(17)
C(13)-C(14)-C(15)	120.98(17)
C(16)-C(15)-C(14)	117.53(16)
C(15)-C(16)-C(11)	121.32(15)
C(15)-C(16)-C(17)	133.79(16)

C(11)-C(16)-C(17)	104.67(14)
O(10)-C(17)-C(16)	101.52(13)
O(10)-C(17)-C(18)	100.64(13)
C(16)-C(17)-C(18)	107.72(13)
C(19)-C(18)-C(17)	114.68(14)
C(19)-C(18)-C(8)	106.61(13)
C(17)-C(18)-C(8)	101.70(13)
O(20)-C(19)-N(21)	125.15(16)
O(20)-C(19)-C(18)	128.21(16)
N(21)-C(19)-C(18)	106.63(14)
C(19)-N(21)-C(22)	136.04(14)
C(19)-N(21)-C(7)	114.52(14)
C(22)-N(21)-C(7)	109.44(13)
C(1)-C(22)-N(21)	130.54(16)
C(1)-C(22)-C(5)	123.30(16)
N(21)-C(22)-C(5)	106.16(14)

Table F – bond lengths and bond angles for **356**

Table 3. Bond lengths [A] and angles [deg] for rt33a1.

C(1)-C(22)	1.3847(16)
C(1)-C(2)	1.3889(17)
C(2)-C(3)	1.3987(19)
C(3)-C(4)	1.3857(18)
C(4)-C(5)	1.3884(16)
C(5)-C(22)	1.4075(15)
C(5)-N(6)	1.4118(15)
N(6)-C(7)	1.2913(15)
C(7)-N(21)	1.3906(14)
C(7)-C(8)	1.4898(16)
C(8)-C(18)	1.5560(16)
C(8)-C(9)	1.5562(16)
C(9)-O(17)	1.4536(14)
C(9)-C(10)	1.5106(17)
C(10)-C(11)	1.3819(17)
C(10)-C(15)	1.3967(16)
C(11)-C(12)	1.3969(19)
C(12)-C(13)	1.3883(19)
C(13)-C(14)	1.3981(17)
C(14)-C(15)	1.3815(16)
C(15)-C(16)	1.5145(15)
C(16)-O(17)	1.4476(14)
C(16)-C(18)	1.5616(16)
C(18)-C(19)	1.5166(16)
C(19)-O(20)	1.2070(14)
C(19)-N(21)	1.3896(14)
N(21)-C(22)	1.3946(14)

C(22)-C(1)-C(2)	115.68(11)
C(1)-C(2)-C(3)	121.74(11)
C(4)-C(3)-C(2)	121.86(11)
C(3)-C(4)-C(5)	117.47(11)
C(4)-C(5)-C(22)	119.72(11)
C(4)-C(5)-N(6)	129.04(11)
C(22)-C(5)-N(6)	111.23(10)
C(7)-N(6)-C(5)	104.19(9)
N(6)-C(7)-N(21)	113.92(10)
N(6)-C(7)-C(8)	136.13(10)
N(21)-C(7)-C(8)	109.96(9)
C(7)-C(8)-C(18)	103.02(9)
C(7)-C(8)-C(9)	117.51(9)
C(18)-C(8)-C(9)	101.02(9)
O(17)-C(9)-C(10)	101.35(9)
O(17)-C(9)-C(8)	100.40(9)
C(10)-C(9)-C(8)	108.50(9)
C(11)-C(10)-C(15)	121.11(11)
C(11)-C(10)-C(9)	133.89(11)
C(15)-C(10)-C(9)	105.00(10)
C(10)-C(11)-C(12)	117.87(11)
C(13)-C(12)-C(11)	120.93(11)
C(12)-C(13)-C(14)	121.07(11)
C(15)-C(14)-C(13)	117.70(11)
C(14)-C(15)-C(10)	121.27(10)
C(14)-C(15)-C(16)	134.04(11)
C(10)-C(15)-C(16)	104.68(10)

O(17)-C(16)-C(15)	101.17(9)
O(17)-C(16)-C(18)	99.80(9)
C(15)-C(16)-C(18)	108.84(9)
C(16)-O(17)-C(9)	96.93(8)
C(19)-C(18)-C(8)	106.86(9)
C(19)-C(18)-C(16)	116.01(9)
C(8)-C(18)-C(16)	101.76(9)
O(20)-C(19)-N(21)	125.42(11)
O(20)-C(19)-C(18)	128.43(11)
N(21)-C(19)-C(18)	106.15(9)
C(19)-N(21)-C(7)	113.99(10)
C(19)-N(21)-C(22)	139.00(10)
C(7)-N(21)-C(22)	106.99(9)
C(1)-C(22)-N(21)	132.81(10)
C(1)-C(22)-C(5)	123.51(11)
N(21)-C(22)-C(5)	103.67(9)

Table G – bond lengths and bond angles for **357**

Table 3. Bond lengths [A] and angles [deg] for rt26a1.

C(1)-C(2)	1.3884(15)
C(1)-C(18)	1.3866(15)
C(1)-H(11)	1.000
C(2)-C(3)	1.4026(16)
C(2)-H(21)	1.000
C(3)-C(4)	1.3860(16)
C(3)-H(31)	1.000
C(4)-C(5)	1.3951(15)
C(4)-H(41)	1.000
C(5)-C(6)	1.4454(15)
C(5)-C(18)	1.4140(14)
C(6)-C(7)	1.3523(15)
C(6)-H(61)	1.000
C(7)-C(8)	1.4927(15)
C(7)-N(17)	1.3986(13)
C(8)-C(9)	1.5718(15)
C(8)-C(14)	1.5590(15)
C(8)-H(81)	1.000
C(9)-C(10)	1.5396(16)
C(9)-C(13)	1.5129(17)
C(9)-H(91)	1.000
C(10)-C(11)	1.5431(17)
C(10)-H(101)	1.000
C(10)-H(102)	1.000
C(11)-C(12)	1.5127(16)
C(11)-C(14)	1.5629(14)
C(11)-H(111)	1.000
C(12)-C(13)	1.3253(18)
C(12)-H(121)	1.000
C(13)-H(131)	1.000
C(14)-C(15)	1.5189(15)
C(14)-H(141)	1.000
C(15)-O(16)	1.2090(14)
C(15)-N(17)	1.3866(13)
N(17)-C(18)	1.3921(13)

C(2)-C(1)-C(18)	117.2(1)
C(2)-C(1)-H(11)	121.42(6)
C(18)-C(1)-H(11)	121.41(6)
C(1)-C(2)-C(3)	121.2(1)
C(1)-C(2)-H(21)	119.42(6)
C(3)-C(2)-H(21)	119.41(6)
C(2)-C(3)-C(4)	121.0(1)
C(2)-C(3)-H(31)	119.48(6)
C(4)-C(3)-H(31)	119.49(6)
C(3)-C(4)-C(5)	119.1(1)
C(3)-C(4)-H(41)	120.43(6)
C(5)-C(4)-H(41)	120.43(6)
C(4)-C(5)-C(6)	133.4(1)
C(4)-C(5)-C(18)	118.6(1)
C(6)-C(5)-C(18)	107.92(9)
C(5)-C(6)-C(7)	107.18(9)
C(5)-C(6)-H(61)	126.39(6)
C(7)-C(6)-H(61)	126.43(6)
C(6)-C(7)-C(8)	141.4(1)

C(6)-C(7)-N(17)	109.26(9)
C(8)-C(7)-N(17)	109.29(9)
C(7)-C(8)-C(9)	117.02(9)
C(7)-C(8)-C(14)	103.50(8)
C(9)-C(8)-C(14)	102.35(8)
C(7)-C(8)-H(81)	106.58(6)
C(9)-C(8)-H(81)	107.67(6)
C(14)-C(8)-H(81)	120.32(5)
C(8)-C(9)-C(10)	99.07(9)
C(8)-C(9)-C(13)	107.09(9)
C(10)-C(9)-C(13)	100.2(1)
C(8)-C(9)-H(91)	114.56(6)
C(10)-C(9)-H(91)	120.32(6)
C(13)-C(9)-H(91)	113.57(6)
C(9)-C(10)-C(11)	93.99(9)
C(9)-C(10)-H(101)	113.15(6)
C(11)-C(10)-H(101)	113.20(6)
C(9)-C(10)-H(102)	113.21(6)
C(11)-C(10)-H(102)	113.20(6)
H(101)-C(10)-H(102)	109.467
C(10)-C(11)-C(12)	100.38(9)
C(10)-C(11)-C(14)	99.69(9)
C(12)-C(11)-C(14)	105.93(8)
C(10)-C(11)-H(111)	119.46(6)
C(12)-C(11)-H(111)	114.32(6)
C(14)-C(11)-H(111)	114.87(6)
C(11)-C(12)-C(13)	107.6(1)
C(11)-C(12)-H(121)	126.21(7)
C(13)-C(12)-H(121)	126.21(7)
C(9)-C(13)-C(12)	108.2(1)
C(9)-C(13)-H(131)	125.94(6)
C(12)-C(13)-H(131)	125.87(7)
C(8)-C(14)-C(11)	103.26(8)
C(8)-C(14)-C(15)	106.44(8)
C(11)-C(14)-C(15)	114.18(9)
C(8)-C(14)-H(141)	116.94(5)
C(11)-C(14)-H(141)	109.64(6)
C(15)-C(14)-H(141)	106.62(5)
C(14)-C(15)-O(16)	128.7(1)
C(14)-C(15)-N(17)	106.37(9)
O(16)-C(15)-N(17)	124.9(1)
C(7)-N(17)-C(15)	114.25(9)
C(7)-N(17)-C(18)	109.61(8)
C(15)-N(17)-C(18)	136.14(9)
C(1)-C(18)-C(5)	122.9(1)
C(1)-C(18)-N(17)	131.10(9)
C(5)-C(18)-N(17)	106.03(9)

Table H – bond lengths and bond angles for **360**

Table 3. Bond lengths [A] and angles [deg] for rt48d3.

C(1)-C(2)	1.5480(17)
C(1)-N(10)	1.4663(15)
C(1)-C(91)	1.5180(15)
C(1)-H(11)	1.000
C(2)-C(3)	1.5110(17)
C(2)-H(21)	1.000
C(2)-H(22)	1.000
O(3)-C(3)	1.2085(15)
C(3)-N(4)	1.3867(14)
N(4)-C(41)	1.3935(14)
N(4)-C(91)	1.3939(15)
C(5)-C(6)	1.3897(17)
C(5)-C(41)	1.3808(17)
C(5)-H(51)	1.000
C(6)-C(7)	1.402(2)
C(6)-H(61)	1.000
C(7)-C(8)	1.3838(19)
C(7)-H(71)	1.000
C(8)-C(81)	1.4009(16)
C(8)-H(81)	1.000
C(9)-C(81)	1.4504(17)
C(9)-C(91)	1.3555(16)
C(9)-H(91)	1.000
N(10)-C(11)	1.4622(16)
N(10)-C(15)	1.4629(16)
C(11)-C(12)	1.5206(18)
C(11)-H(111)	1.000
C(11)-H(112)	1.000
C(12)-C(13)	1.519(2)
C(12)-H(121)	1.000
C(12)-H(122)	1.000
C(13)-C(14)	1.519(2)
C(13)-H(131)	1.000
C(13)-H(132)	1.000
C(14)-C(15)	1.5208(18)
C(14)-H(141)	1.000
C(14)-H(142)	1.000
C(15)-H(151)	1.000
C(15)-H(152)	1.000
C(41)-C(81)	1.4132(16)

C(2)-C(1)-N(10)	111.19(9)
C(2)-C(1)-C(91)	102.29(9)
N(10)-C(1)-C(91)	115.76(9)
C(2)-C(1)-H(11)	115.439
N(10)-C(1)-H(11)	101.878
C(91)-C(1)-H(11)	110.837
C(1)-C(2)-C(3)	107.51(9)
C(1)-C(2)-H(21)	109.959
C(3)-C(2)-H(21)	109.959
C(1)-C(2)-H(22)	109.959
C(3)-C(2)-H(22)	109.959
H(21)-C(2)-H(22)	109.467
C(2)-C(3)-O(3)	128.9(1)
C(2)-C(3)-N(4)	106.0(1)

O(3)-C(3)-N(4)	125.08(11)
C(3)-N(4)-C(41)	135.67(11)
C(3)-N(4)-C(91)	114.4(1)
C(41)-N(4)-C(91)	109.84(9)
C(6)-C(5)-C(41)	116.77(11)
C(6)-C(5)-H(51)	121.613
C(41)-C(5)-H(51)	121.613
C(5)-C(6)-C(7)	120.78(12)
C(5)-C(6)-H(61)	119.608
C(7)-C(6)-H(61)	119.608
C(6)-C(7)-C(8)	121.93(11)
C(6)-C(7)-H(71)	119.036
C(8)-C(7)-H(71)	119.037
C(7)-C(8)-C(81)	118.49(12)
C(7)-C(8)-H(81)	120.757
C(81)-C(8)-H(81)	120.757
C(81)-C(9)-C(91)	106.9(1)
C(81)-C(9)-H(91)	126.534
C(91)-C(9)-H(91)	126.534
C(1)-N(10)-C(11)	111.90(9)
C(1)-N(10)-C(15)	114.01(9)
C(11)-N(10)-C(15)	110.10(9)
N(10)-C(11)-C(12)	110.08(11)
N(10)-C(11)-H(111)	109.320
C(12)-C(11)-H(111)	109.320
N(10)-C(11)-H(112)	109.320
C(12)-C(11)-H(112)	109.320
H(111)-C(11)-H(112)	109.467
C(11)-C(12)-C(13)	110.82(12)
C(11)-C(12)-H(121)	109.134
C(13)-C(12)-H(121)	109.134
C(11)-C(12)-H(122)	109.134
C(13)-C(12)-H(122)	109.134
H(121)-C(12)-H(122)	109.466
C(12)-C(13)-C(14)	110.57(12)
C(12)-C(13)-H(131)	109.196
C(14)-C(13)-H(131)	109.196
C(12)-C(13)-H(132)	109.197
C(14)-C(13)-H(132)	109.196
H(131)-C(13)-H(132)	109.467
C(13)-C(14)-C(15)	110.92(12)
C(13)-C(14)-H(141)	109.108
C(15)-C(14)-H(141)	109.109
C(13)-C(14)-H(142)	109.108
C(15)-C(14)-H(142)	109.109
H(141)-C(14)-H(142)	109.466
N(10)-C(15)-C(14)	109.56(11)
N(10)-C(15)-H(151)	109.449
C(14)-C(15)-H(151)	109.450
N(10)-C(15)-H(152)	109.450
C(14)-C(15)-H(152)	109.450
H(151)-C(15)-H(152)	109.467
N(4)-C(41)-C(5)	130.25(11)
N(4)-C(41)-C(81)	105.9(1)
C(5)-C(41)-C(81)	123.8(1)
C(8)-C(81)-C(9)	133.83(11)
C(8)-C(81)-C(41)	118.23(11)
C(9)-C(81)-C(41)	107.9(1)
C(1)-C(91)-N(4)	108.94(9)

C(1)-C(91)-C(9)	141.71(11)
N(4)-C(91)-C(9)	109.3(1)

Table I – bond lengths and bond angles for **375**

Table 3. Bond lengths [A] and angles [deg] for rt54a2.

S(1)-C(1)	1.840(3)
S(1)-C(10)	1.775(3)
C(1)-C(2)	1.544(4)
C(1)-C(91)	1.494(3)
C(1)-H(11)	1.000
C(2)-C(3)	1.519(4)
C(2)-H(21)	1.000
C(2)-H(22)	1.001
C(3)-O(3)	1.204(3)
C(3)-N(4)	1.386(3)
N(4)-C(41)	1.393(3)
N(4)-C(91)	1.401(3)
C(41)-C(5)	1.383(3)
C(41)-C(81)	1.412(3)
C(5)-C(6)	1.386(4)
C(5)-H(51)	1.001
C(6)-C(7)	1.393(4)
C(6)-H(61)	1.000
C(7)-C(8)	1.391(4)
C(7)-H(71)	1.000
C(8)-C(81)	1.396(3)
C(8)-H(81)	1.001
C(81)-C(9)	1.452(3)
C(9)-C(91)	1.352(3)
C(9)-H(91)	1.001
C(10)-C(11)	1.387(4)
C(10)-C(15)	1.391(4)
C(11)-C(12)	1.390(4)
C(11)-H(111)	1.000
C(12)-C(13)	1.379(5)
C(12)-H(121)	1.000
C(13)-C(14)	1.380(4)
C(13)-H(131)	1.001
C(14)-C(15)	1.384(4)
C(14)-H(141)	1.001
C(15)-H(151)	1.001
S(101)-C(101)	1.831(3)
S(101)-C(110)	1.776(3)
C(101)-C(102)	1.551(4)
C(101)-C(191)	1.504(3)
C(101)-H(1011)	1.000
C(102)-C(103)	1.512(4)
C(102)-H(1021)	1.000
C(102)-H(1022)	1.000
C(103)-O(103)	1.213(3)
C(103)-N(104)	1.385(3)
N(104)-C(141)	1.398(3)
N(104)-C(191)	1.397(3)
C(141)-C(105)	1.382(4)
C(141)-C(115)	1.411(3)
C(105)-C(106)	1.386(4)
C(105)-H(1051)	1.000
C(106)-C(107)	1.405(4)
C(106)-H(1061)	1.001
C(107)-C(108)	1.384(4)

C(107)-H(1071)	1.001
C(108)-C(115)	1.395(4)
C(108)-H(1081)	1.000
C(181)-C(110)	1.384(4)
C(181)-C(114)	1.388(4)
C(181)-H(1811)	1.001
C(115)-C(109)	1.446(3)
C(109)-C(191)	1.346(3)
C(109)-H(1091)	1.001
C(110)-C(111)	1.388(4)
C(111)-C(112)	1.386(4)
C(111)-H(1111)	1.000
C(112)-C(113)	1.387(4)
C(112)-H(1121)	1.000
C(113)-C(114)	1.377(4)
C(113)-H(1131)	1.001
C(114)-H(1141)	1.001

C(1)-S(1)-C(10)	101.22(12)
S(1)-C(1)-C(2)	107.24(18)
S(1)-C(1)-C(91)	112.03(17)
C(2)-C(1)-C(91)	103.5(2)
S(1)-C(1)-H(11)	107.536
C(2)-C(1)-H(11)	115.512
C(91)-C(1)-H(11)	111.015
C(1)-C(2)-C(3)	106.7(2)
C(1)-C(2)-H(21)	110.166
C(3)-C(2)-H(21)	110.235
C(1)-C(2)-H(22)	110.131
C(3)-C(2)-H(22)	110.179
H(21)-C(2)-H(22)	109.364
C(2)-C(3)-O(3)	128.4(2)
C(2)-C(3)-N(4)	106.2(2)
O(3)-C(3)-N(4)	125.3(3)
C(3)-N(4)-C(41)	136.2(2)
C(3)-N(4)-C(91)	114.0(2)
C(41)-N(4)-C(91)	109.8(2)
N(4)-C(41)-C(5)	130.4(2)
N(4)-C(41)-C(81)	105.9(2)
C(5)-C(41)-C(81)	123.7(2)
C(41)-C(5)-C(6)	116.7(2)
C(41)-C(5)-H(51)	121.618
C(6)-C(5)-H(51)	121.675
C(5)-C(6)-C(7)	121.3(3)
C(5)-C(6)-H(61)	119.333
C(7)-C(6)-H(61)	119.386
C(6)-C(7)-C(8)	121.4(2)
C(6)-C(7)-H(71)	119.305
C(8)-C(7)-H(71)	119.282
C(7)-C(8)-C(81)	118.8(2)
C(7)-C(8)-H(81)	120.624
C(81)-C(8)-H(81)	120.581
C(41)-C(81)-C(8)	118.1(2)
C(41)-C(81)-C(9)	108.1(2)
C(8)-C(81)-C(9)	133.8(2)
C(81)-C(9)-C(91)	107.0(2)
C(81)-C(9)-H(91)	126.504
C(91)-C(9)-H(91)	126.501
C(1)-C(91)-N(4)	109.1(2)

C(1)-C(91)-C(9)	141.7(2)
N(4)-C(91)-C(9)	109.2(2)
S(1)-C(10)-C(11)	119.0(2)
S(1)-C(10)-C(15)	120.8(2)
C(11)-C(10)-C(15)	120.2(3)
C(10)-C(11)-C(12)	119.3(3)
C(10)-C(11)-H(111)	120.300
C(12)-C(11)-H(111)	120.351
C(11)-C(12)-C(13)	120.3(3)
C(11)-C(12)-H(121)	119.857
C(13)-C(12)-H(121)	119.815
C(12)-C(13)-C(14)	120.2(3)
C(12)-C(13)-H(131)	119.815
C(14)-C(13)-H(131)	119.951
C(13)-C(14)-C(15)	120.0(3)
C(13)-C(14)-H(141)	119.996
C(15)-C(14)-H(141)	119.962
C(10)-C(15)-C(14)	119.8(3)
C(10)-C(15)-H(151)	120.052
C(14)-C(15)-H(151)	120.169
C(101)-S(101)-C(110)	101.94(12)
S(101)-C(101)-C(102)	107.57(17)
S(101)-C(101)-C(191)	111.96(18)
C(102)-C(101)-C(191)	103.1(2)
S(101)-C(101)-H(1011)	107.224
C(102)-C(101)-H(1011)	115.600
C(191)-C(101)-H(1011)	111.414
C(101)-C(102)-C(103)	106.9(2)
C(101)-C(102)-H(1021)	110.076
C(103)-C(102)-H(1021)	110.127
C(101)-C(102)-H(1022)	110.094
C(103)-C(102)-H(1022)	110.151
H(1021)-C(102)-H(1022)	109.419
C(102)-C(103)-O(103)	128.5(2)
C(102)-C(103)-N(104)	106.0(2)
O(103)-C(103)-N(104)	125.6(3)
C(103)-N(104)-C(141)	135.8(2)
C(103)-N(104)-C(191)	114.7(2)
C(141)-N(104)-C(191)	109.4(2)
N(104)-C(141)-C(105)	130.2(2)
N(104)-C(141)-C(115)	106.0(2)
C(105)-C(141)-C(115)	123.8(2)
C(141)-C(105)-C(106)	116.9(3)
C(141)-C(105)-H(1051)	121.566
C(106)-C(105)-H(1051)	121.582
C(105)-C(106)-C(107)	120.5(3)
C(105)-C(106)-H(1061)	119.712
C(107)-C(106)-H(1061)	119.764
C(106)-C(107)-C(108)	122.0(2)
C(106)-C(107)-H(1071)	119.029
C(108)-C(107)-H(1071)	118.931
C(107)-C(108)-C(115)	118.4(2)
C(107)-C(108)-H(1081)	120.808
C(115)-C(108)-H(1081)	120.752
C(110)-C(181)-C(114)	120.6(3)
C(110)-C(181)-H(1811)	119.660
C(114)-C(181)-H(1811)	119.711
C(141)-C(115)-C(108)	118.3(2)
C(141)-C(115)-C(109)	107.8(2)

C(108)-C(115)-C(109)	133.8(2)
C(115)-C(109)-C(191)	107.4(2)
C(115)-C(109)-H(1091)	126.324
C(191)-C(109)-H(1091)	126.274
C(101)-C(191)-N(104)	108.6(2)
C(101)-C(191)-C(109)	142.0(2)
N(104)-C(191)-C(109)	109.4(2)
S(101)-C(110)-C(181)	121.7(2)
S(101)-C(110)-C(111)	118.8(2)
C(181)-C(110)-C(111)	119.5(3)
C(110)-C(111)-C(112)	119.6(3)
C(110)-C(111)-H(1111)	120.194
C(112)-C(111)-H(1111)	120.181
C(111)-C(112)-C(113)	120.7(3)
C(111)-C(112)-H(1121)	119.660
C(113)-C(112)-H(1121)	119.686
C(112)-C(113)-C(114)	119.7(3)
C(112)-C(113)-H(1131)	120.147
C(114)-C(113)-H(1131)	120.171
C(181)-C(114)-C(113)	119.9(3)
C(181)-C(114)-H(1141)	120.105
C(113)-C(114)-H(1141)	120.024

Table J – bond lengths and bond angles for **381**